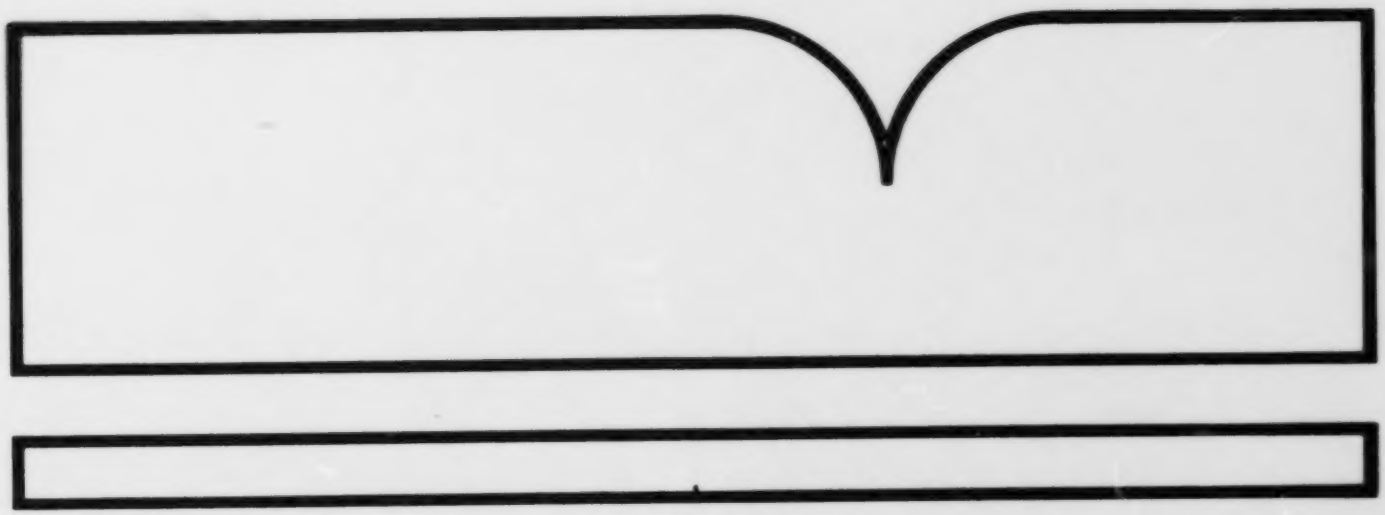
PB81-117319

Ambient Water Quality Criteria for Antimony

(U.S.) Environmental Protection Agency
Washington, DC

Oct 80



U.S. Department of Commerce
National Technical Information Service
NTIS

United States
Environmental Protection
Agency

Office of Water
Regulations and Standards
Criteria and Standards Division
Washington DC 20460

EPA 440/5-80-020
October 1980

PB81-117319

EPA

Ambient Water Quality Criteria for Antimony

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO. PB81 117319
4. TITLE AND SUBTITLE Ambient Water Quality Criteria for: Antimony		5. REPORT DATE October, 1980 6. PERFORMING ORGANIZATION CODE NTISEPAOWP
7. AUTHOR(S) Environmental Criteria and Assessment Office		8. PERFORMING ORGANIZATION REPORT NO. EPA-440/5-80-020
9. PERFORMING ORGANIZATION NAME AND ADDRESS Office of Water Regulations and Standards Criteria and Standards Division U.S. Environmental Protection Agency Washington, D.C. 20460		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Same as box 9		13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES
Supersedes draft document PB 296 789

16. ABSTRACT
Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Antimony. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
For Public Release	Unclassified	
	20. SECURITY CLASS *(This page)*	22. PRICE
	Unclassified	

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

AMBIENT WATER QUALITY CRITERIA FOR

ANTIMONY

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Water Regulations and Standards
Criteria and Standards Division
Washington, D.C.

Office of Research and Development
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Carcinogen Assessment Group
Washington, D.C.

Environmental Research Laboratories
Corvalis, Oregon
Duluth, Minnesota
Gulf Breeze, Florida
Narragansett, Rhode Island

DISCLAIMER

This report has been reviewed by the Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

AVAILABILITY NOTICE

This document is available to the public through the National Technical Information Service, (NTIS), Springfield, Virginia 22161.

FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
Deputy Assistant Administrator
Office of Water Regulations and Standards

ACKNOWLEDGEMENTS

Aquatic Life Toxicology:

Charles E. Stephan, ERL-Duluth
U.S. Environmental Protection Agency

John E. Gentile, ERL-Narragansett
U.S. Environmental Protection Agency

Mammalian Toxicology and Human Health Effects:

Paul Mushak (author)
University of North Carolina

Christopher T. DeRosa (doc. mgr.)
ECAO-Cin
U.S. Environmental Protection Agency

Jerry F. Stara (doc. mgr.) ECAO-Cin
U.S. Environmental Protection Agency

Paul B. Hammond
University of Cincinnati

Magnus Piscator
Karolinska Institute

William B. Buck
University of Illinois

Edward Calabrese
University of Massachusetts

Patrick Durkin
Syracuse Research Corp.

Si Duk Lee, ECAO-Cin
U.S. Environmental Protection Agency

Technical Support Services Staff: D.J. Reisman, M.A. Garlough, B.L. Zwayer, P.A. Daunt, K.S. Edwards, T.A. Scandura, A.T. Pressley, C.A. Cooper, M.M. Denessen.

Clerical Staff: C.A. Haynes, S.J. Faehr, L.A. Wade, D. Jones, B.J. Bordicks, B.J. Quesnell, T. Highland, B. Gardiner, R. Swantack.

TABLE OF CONTENTS

	Page
Criteria Summary	
Introduction	A-1
Aquatic Life Toxicology	B-1
Introduction	B-1
Effects	B-1
Acute Toxicity	B-1
Chronic Toxicity	B-2
Plant Effects	B-3
Residues	B-3
Miscellaneous	B-3
Summary	B-3
Criteria	B-4
References	B-11
Mammalian Toxicology and Human Health Effects	C-1
Introduction	C-1
Exposure	C-3
Ingestion from Water	C-4
Ingestion from Food	C-4
Inhalation	C-6
Integrated Multimedia Exposure Estimates	C-6
Pharmacokinetics	C-7
Absorption	C-7
Distribution	C-10
Metabolism	C-19
Excretion	C-21
Effects	C-22
Acute, Subacute, and Chronic Toxicity	C-23
Mutagenicity and Carcinogenicity	C-27
Respiratory System Effects	C-28
Cardiovascular System Effects	C-32
Blood Effects	C-34
Liver, Kidney, Spleen and Adrenal Effects	C-34
Reproduction, Development and Longevity	C-36
Skin and Eye Effects	C-38
Summary of Animal Toxicology	C-38
Human Health Effects	C-39
Therapeutic Uses	C-39
Effects on the Gastrointestinal System	C-40
Effects on the Hepatic System	C-41
Effects on the Cardiovascular System	C-41
Effects on the Skin	C-48
Other Effects	C-49
Summary of Therapeutic Use Effects	C-49
Industrial Exposures	C-50
Respiratory and Dermal Effects	C-53
Myocardial Effects	C-58

Carcinogenis C-59
Blood Effects C-60
Reproduction and Development Effects C-60
Criteria Formulation C-62
Existing Guidelines and Standards C-62
Special Groups at Risk C-63
Basis for the Criterion C-65
Summary of Health Effects C-65
Dose-Effect/Dose Response Relationships C-67
References C-72

CRITERION DOCUMENT

ANTIMONY

CRITERIA

Aquatic Life

The available data for antimony indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 9,000 and 1,600 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested. Toxicity to algae occurs at concentrations as low as 610 µg/l.

No saltwater organisms have been adequately tested with antimony, and no statement can be made concerning acute or chronic toxicity.

Human Health

For the protection of human health from the toxic properties of antimony ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 146 µg/l.

For the protection of human health from the toxic properities of antimony ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 45 mg/l.

INTRODUCTION

Antimony, a silvery, brittle solid, belongs to group VB of the periodic table and lies between arsenic and bismuth. It is classified as both a metal and a metalloid. It has an atomic number of 51 and an atomic weight of 121.8, and its principal oxidation states are +3 and +5.

Antimony reacts with both sulfur and chlorine to form the triand pentavalent sulfides and chlorides. Oxidation to antimony trioxide, the major commercial oxide of antimony, is achieved under controlled conditions. Stibine, antimony trihydride, is formed by the reduction of antimony compounds in acid media using zinc or other reducing metals.

Solubilities of antimony compounds range from insoluble to fully soluble. Most inorganic compounds of antimony are either only slightly water soluble or decompose in aqueous media. Antimonials such as potassium antimony tartrate, in which organic ligands are bound to the element and employed therapeutically, are water soluble.

The brittle character of antimony metal precludes rolling, forging, or drawing but accounts for improved hardness and lowered melting point in alloys with lead, bismuth, tin, copper, nickel, iron, and cobalt. In particular, the metal is heavily employed in antimonial lead, in bearings, and in ammunition.

The most important antimony compound in commerce is probably antimony trioxide, a colorless, insoluble powder, the properties of which place it in high demand as a flame retarding agent for many commodities. It is insoluble in water and dilute nitric or sulfuric acids but is soluble in hydrochloric and certain organic acids. It dissolves in bases to give antimonate.

A second form of antimony having commercial usefulness is antimony trisulfide, Sb_2S_3, which is converted to the trioxide for use as a flame

retardant. Other uses are in the manufacture of fireworks and matches. Antimony trisulfide is insoluble in water but dissolves in concentrated hydrochloric acid with the evolution of hydrogen sulfide. It is also soluble in strong alkali solution.

Antimony shows some definite cationic behavior but only in the trivalent state. For example, antimony (III) forms complexes with inorganic and organic acids to produce antimonial salts such as the disulfate $(Sb(SO_4)_2)^-$, the dioxalate $Sb(C_2O_4)^{-2}$ and the well known tartrate, $(Sb(OH)C_4H_3O_5)^-$ (Weast, 1977; Windholz, 1976).

Antimony is a naturally occurring element which comprises between 0.2 and 0.5 ppm of the earth's crust. Environmental concentrations of antimony at 35 parts per thousand of salinity are reported as 0.33 µg/l in seawater and as 1.1 µg/l in freshwater streams.

In the environment antimony may enter aquatic systems from natural weathering of rocks, runoff from soils, and effluents from mining and manufacturing operations, as well as municipal and industrial discharges. Antimony concentrations are generally in the low ppm range for uncontaminated sediments, while sediments within 1 km of a copper smelter have shown levels of several thousand ppm (Crecelius, et al. 1975).

Certain antimonial complexes undergo hydrolysis or oxidations reactions and consequently are not long-lived in the environment. Both the oxide of antimony and the trihalides are volatile compounds, while antimony trichloride releases hydrogen chloride gas in the presence of moisture (U.S. EPA, 1976). Antimony trioxide can undergo photo-reduction in the presence of ultraviolet light in aqueous solutions (Markham, et al. 1958).

Several metals surrounding antimony in the periodic table undergo the methylation of inorganic compounds by microorganisms to yield organometallic

compounds that are stable and mobile in water and air. Parris and Brinckman (1976) report that although no obvious thermodynamic or kinetic barrier prevents this reaction, biological methylation of antimony has not been demonstrated.

REFERENCES

Crecelius, E.A., et al. 1975. Geochemistries and arsenic, antimony, mercury, and related elements in sediments of Puget Sound. Environ. Sci. Technol. 9: 325.

Markham, M.D., et al. 1958. Photochemical properties of antimony trioxide. Jour. Phys. Chem. 62: 989.

Parris, G.E. and F.E. Brinckman. 1976. Reactions which relate to environmental mobility of arsenic and antimony. II: Oxidation of trimethyarsine and trimethylstibine. Environ. Sci. Technol. 10: 1128.

U.S. EPA. 1976. Literature study of selected potential environmental contaminants. Antimony and its compounds. EPA-550/2-76-002. Off. Tox. Subst. Washington, D.C.

Weast, R.C. 1977. CRC Handbook of Chemistry and Physics. 58th ed. CRC Press, Inc. Cleveland, Ohio.

Windholz, M. (ed.), 1976. The Merck Index. 9th ed. Merck and Co., Inc. Rahway, New Jersey.

Aquatic Life Toxicology*

INTRODUCTION

Antimony exists in three valence states (-3, +3, and +5), but the -3 state is not stable in oxygenated water. For the +3 state, antimony trioxide is not very soluble in water. On the other hand, antimony trichloride is very soluble, but it will form the insoluble antimony oxychloride. The +3 state also forms water soluble complexes with some acids, such as in potassium antimony tartrate. Little seems to be known about the aqueous chemistry of the +5 valence state.

The data base for antimony and freshwater organisms is small and indicates that plants may be more sensitive than fish or invertebrate species. There are no data to evaluate the effect of water quality on the toxicity of antimony.

The saltwater data base is limited to the results of four tests with antimony trioxide.

All test results are expressed in terms of the metal.

EFFECTS

Acute Toxicity

The acute toxicity to Daphnia magna has been determined by four investigators using three different antimony compounds. Anderson (1948) determined a 64-hour EC_{50} of 19,800 µg/l for antimony trichloride (Table 6). The 48-hour value for antimony potassium tartrate was 9,000 µg/l (Table 1).

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

Kimball (Manuscript) tested Daphnia magna and antimony trichloride with and without feeding and calculated 48-hour LC_{50} values of 12,100 and 18,800 µg/l, respectively (Tables 1 and 6). Test concentrations were measured in the last two tests. These data for Daphnia magna indicate that feeding procedures and the use of three different antimony compounds did not, if at all, significantly affect toxicity. The species acute value for Daphnia magna is 18,800 µg/l (Table 1). The 96-hour LC_{50} for the fathead minnow is 21,900 µg/l for antimony trichloride (Kimball, Manuscript).

Tests with antimony trioxide and the bluegill and Daphnia magna resulted in 50 percent effect levels greater than 530,000 µg/l (Table 6).

No lethal effect on the saltwater mysid shrimp, Mysidopsis bahia, was observed after 96 hours at static test concentrations as high as 4,200 µg/l (Table 6). The 96-hour LC_{50} for the sheepshead minnow is between 6,200 and 8,300 µg/l (Table 6).

Chronic Toxicity

A life cycle test with Daphnia magna and antimony trichloride produced limits of 4,200 and 7,000 µg/l for a chronic value of 5,400 µg/l (Table 2).

No adverse effects on the fathead minnow (U.S. EPA, 1978) were observed during an embryo-larval test with antimony trioxide at the highest test concentration of 7.5 µg/l (Table 2). However, a comparable test with antimony trichloride (Kimball, Manuscript) produced limits of 1,100 and 2,300 µg/l for a chronic value of 1,600 µg/l.

The acute-chronic ratios for the cladoceran and the fathead minnow were 3.5 and 14, respectively (Table 2). These results provide a geometric mean acute-chronic ratio of 7.0.

The species mean acute and chronic values are summarized in Table 3.

No chronic test has been conducted with a saltwater species.

Plant Effects

The 96-hour EC_{50} values for chlorophyll *a* inhibition and reduction in cell numbers of the alga, *Selenastrum capricornutum*, are 610 and 630 µg/l, respectively (Table 4). These results indicate that aquatic plants may be more sensitive than fish and invertebrate species.

No inhibition of chlorophyll *a* or reduction in cell numbers of the alga, *Skeletonema costatum*, were observed at concentrations as high as 4,200 µg/l (Table 4).

Residues

There was no detectable bioconcentration of antimony by the bluegill above control concentrations during a 28-day exposure to antimony trioxide (Table 5).

Miscellaneous

The data in Table 6 have been discussed previously.

Summary

There are insufficient data to determine whether or not water quality affects the toxicity of antimony to freshwater or saltwater aquatic life. Tests with antimony potassium tartrate and antimony trichloride and *Daphnia magna* suggest no difference in toxicity between these compounds. No acute toxicity was observed for the less soluble antimony trioxide and this same species. The LC_{50} and EC_{50} values for *Daphnia magna* and the fathead minnow ranged from 9,000 to 21,900 µg/l. Chronic values and acute-chronic ratios (in parentheses) for the fathead minnow and *Daphnia magna* were 1,600 (14) and 5,400 µg/l (3.5), respectively. The freshwater alga, *Selenastrum capricornutum*, was more sensitive than the tested animal species with a 96-hour EC_{50} for inhibition of chlorophyll *a* of 610 µg/l. Whole body analysis of bluegill demonstrated no uptake beyond that present in control fish.

Several tests have been conducted with saltwater species and antimony trioxide, but no definitive data resulted.

CRITERIA

The available data for antimony indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 9,000 and 1,600 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested. Toxicity to algae occurs at concentrations as low as 610 µg/l.

No saltwater organisms have been adequately tested with antimony, and no statement can be concerning acute or chronic toxicity.

Table 1. Acute values for antimony

Species	Method*	Chemical	LC50/EC50 (µg/l)**	Species Mean Acute Value (µg/l)**	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	S, U	Antimony potassium tartrate	9,000	9,000	Bringman & Kuhn, 1959
Cladoceran, *Daphnia magna*	S, M	Antimony trichloride	18,800	18,800	Kimball, Manuscript
Fathead minnow, *Pimephales promelas*	FT, M	Antimony trichloride	21,900	21,900	Kimball, Manuscript

* S = static, FT = flow-through, U = unmeasured, M = measured

**Results are expressed as antimony, not in terms of the compound.

No Final Acute Value is calculable since the minimum data base requirements are not met.

Table 2. Chronic values for antimony

Species	Method*	Chemical	Limits (µg/l)**	Chronic Value (µg/l)**	Reference
		FRESHWATER SPECIES			
Cladoceran, Daphnia magna	LC	Antimony trichloride	4,200-7,000	5,400	Kimball, Manuscript
Fathead minnow, Pimephales promelas	E-L	Antimony trioxide	>7.5	-	U.S. EPA, 1978
Fathead minnow, Pimephales promelas	E-L	Antimony trichloride	1,100-2,500	1,600	Kimball, Manuscript

* LC = life cycle, E-L = embryo-larval

**Results are expressed as antimony, not in terms of the compound.

Acute-Chronic Ratios

Species	Chemical	Chronic Value (µg/l)	Acute Value (µg/l)	Ratio
Cladoceran, Daphnia magna	Antimony trichloride	5,400	18,800	3.5
Fathead minnow, Pimephales promelas	Antimony trichloride	1,600	21,900	14

Geometric mean acute-chronic ratio = 7.0

Table 3. Species mean acute and chronic values for antimony

Number	Species	Species Mean Acute Value* (µg/l)	Species Mean Chronic Value (µg/l)	Acute-Chronic Ratio**
		FRESHWATER SPECIES		
2	Fathead minnow, *Pimephales promelas*	21,900	1,600	14
1	Cladoceran, *Daphnia magna*	18,800	5,400	3.5

* Rank from high concentration to low concentration by species mean acute value.

**See the Guidelines for derivation of this ratio.

Table 4. Plant values for antimony (U.S. EPA, 1978)

Species	Chemical	Effect	Result (µg/l)*
	FRESHWATER SPECIES		
Alga, *Selenastrum capricornutum*	Antimony trioxide	96-hr EC50 for chlorophyll *a* inhibition	610
Alga, *Selenastrum capricornutum*	Antimony trioxide	96-hr EC50 for reduction in cell numbers	630
	SALTWATER SPECIES		
Alga, *Skeletonema costatum*	Antimony trioxide	96-hr EC50 for chlorophyll *a* inhibition	>4,200
Alga, *Skeletonema costatum*	Antimony trioxide	96-hr EC50 for reduction in cell numbers	>4,200

* Results are expressed as antimony, not in terms of the compound.

Table 5. Residues for antimony (U.S. EPA, 1978)

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)
		FRESHWATER SPECIES		
Bluegill, *Lepomis macrochirus*	whole body	Antimony trioxide	<1	28

Table 6. Other data for antimony

Species	Chemical	Duration	Effect	Result (µg/l)*	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	Antimony trichloride	64 hrs	EC50	19,800	Anderson, 1948
Cladoceran, *Daphnia magna*	Antimony trioxide	48 hrs	EC50	>530,000	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	Antimony trichloride	48 hrs	EC50	12,100**	Kimball, Manuscript
Bluegill, *Lepomis macrochirus*	Antimony trioxide	96 hrs	LC50	>530,000	U.S. EPA, 1978
		SALTWATER SPECIES			
Mysid shrimp, *Mysidopsis bahia*	Antimony trioxide	96 hrs	LC50	>4,200	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	Antimony trioxide	96 hrs	LC50	>6,200 <8,300	U.S. EPA, 1978

* Results are expressed as antimony, not in terms of the compound.

**Animals fed.

REFERENCES

Anderson, B.G. 1948. The apparent thresholds of toxicity to Daphnia magna for chlorides of various metals when added to Lake Erie water. Trans. Am. Fish. Soc. 78: 96.

Bringman, G. and R. Kuhn. 1959. Comparative watertoxicology investigations on bacteria, algae, and daphnids. Ges. Ind. 80: 115.

Kimball, G. Acute and chronic effects of lesser known metals and one organic on fathead minnows (Pimephales promelas) and Daphnia magna. (Manuscript)

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency, Contract No. 68-01-4646.

Mammalian Toxicology and Human Health Effects

INTRODUCTION

A number of biological and adverse health effects in humans and experimental animals are known to be caused by antimony in its various chemical states. Most reported effects in man arise from either occupational exposure to antimony in the course of its mining, industrial processing, and commercial use or as side effects seen with the medicinal use of antimonials as therapeutic agents in inducing emesis or for the treatment of schistosomiasis, leishmaniasis, trypanosomiasis, and ulcerative granuloma. Aside from several acute poisoning episodes occurring within the context of such use, however, the toxicological threat posed by antimony to the general public appears to be quite low. This is due in large part to the very limited amounts of the element that have thus far entered into environmental media that represent potential routes of exposure for humans.

The present document opens with an initial discussion of the chemistry of antimony relevant to environmental exposures or effects on organisms; this is followed by discussion of sources of exposure and the pharmacokinetics of antimony -- absorption, distribution, biological half-time(s), and excretion. Concise comment ensues regarding certain *in vitro* and *in vivo* effects of antimony observed at the biochemical, subcellular, and cellular level; the systemic toxicity of antimony, as delineated in animal toxicology studies; and effects exerted by antimony on man. Lastly, various factors of utility in the development of criterion rationale for standard setting purposes are discussed.

Antimony, a silvery, brittle solid, belongs to group VB of the periodic table and lies between arsenic and bismuth. It is classified as both a metal and a metalloid. It has an atomic number of 51 and an atomic weight of 121.8, and its principal oxidation states are +3 and +5.

Antimony reacts with both sulfur and chlorine to form the tri- and pentavalent sulfides and chlorides. Oxidation to antimony trioxide, the major commercial oxide of antimony, is achieved under controlled conditions. Stibine, antimony trihydride, is formed by the reduction of antimony compounds in acid media using zinc or other reducing metals.

Solubilities of antimony compounds range from insoluble to fully soluble. Most inorganic compounds of antimony are either only slightly water soluble or decompose in aqueous media. Antimonials such as potassium antimony tartrate, in which organic ligands are bound to the element and employed therapeutically, are water soluble.

The brittle character of antimony metal precludes rolling, forging, or drawing but accounts for improved hardness and lowered melting point in alloys with lead, bismuth, tin, copper, nickel, iron, and cobalt. In particular, the metal is heavily employed in antimonial lead which is used in bearings and in ammunition.

The most important antimony compound in commerce is probably antimony trioxide, a colorless, insoluble powder, the properties of which place it in high demand as a flame-retarding agent for many commodities. It is insoluble in water and dilute nitric or sulfuric acids but is soluble in hydrochloric and certain organic acids. It dissolves in bases to give antimonate.

A second form of antimony having commercial use is antimony trisulfide, Sb_2S_3, which is converted to the trioxide for use as a fire retardant. Other uses are in the manufacture of fireworks and matches. Antimony trisulfide is insoluble in water but dissolves in concentrated hydrochloric acid with the evolution of hydrogen sulfide. It is also soluble in strong alkali solution.

Antimony shows some definite cationic behavior but only in the trivalent state. For example, antimony forms complexes with inorganic and organic acids to produce antimonial salts such as the disulfate $[Sb(SO_4)_2]^-$, the dioxalate $Sb(C_2O_4)^{-2}$, and the well known tartrate, $[Sb(OH)C_4H_3O_5]^-$.

EXPOSURE

Consumption of antimony in the United States is of the order of 40,000 metric tons per year (Callaway, 1969), of which half is obtained from recycled scrap and the balance mainly imported from countries such as Bolivia. Use in the United States is directed chiefly to the manufacture of ammunition, storage batteries, and fire-proofing of textiles.

It is not possible to quantitatively estimate the impact of antimony use on various compartments of the environment which are exposure sources for man. A more meaningful approach is to consider levels of antimony in those media with which human populations come in contact. Of the two major antimony production sites in the U.S. only the one at Laredo, Texas, uses processes that entail any loss to ambient air. Improvements in emissions control have considerably reduced but not eliminated the air levels in the vicinity of the smelter. The second production operation, employing alkali

leachates of Ag-Cu ore and subsequent electrowinning, recycles much of its effluent-borne antimony with apparent minor loss to the environment (Arthur D. Little Co., Inc., 1978). Other, more general, sources of airborne antimony include fossil fuel combustion and municipal incineration.

Ingestion from Water

Schroeder (1966) compiled data from surveys of municipal water supplies in 94 cities and reported that levels were on average less than 0.2 µg/l (0.2 parts per billion) when measured in tap water. In a related study, Schroeder and Kraemer (1974) noted that tap water levels can be increased in soft water supplies owing to the leaching of antimony from plumbing. This would mainly be reflected in 'first-draw' water. The source of antimony in plumbing material would be that present in copper tubing (0.005 percent) and galvanized iron (0.001 percent).

Ingestion from Food

It is far from clear what the average daily dietary intake of antimony is in the U.S. population. Wide-ranging values have been reported over the years.

The comprehensive results of the U.S. Food and Drug Administration's (FDA) survey of various trace metals including antimony in various food classes, using neutron activation analysis, have recently been reported by Tanner and Friedmann (1977). The median level and range of antimony levels for the food classes, expressed as parts per million, wet weight, are: dairy products, $<$ 0.004, $<$ 0.002 to 0.02; meat, fish and poultry, 0.008, $<$ 0.004 to 0.015; grain and cereal products, $<$ 0.01, 0.006 to 0.05; leafy vegetables, $<$ 0.006, 0.001 to 0.027; legume vegetables, 0.008, $<$ 0.002 to 0.014; garden fruits, $<$ 0.006, 0.002 to 0.011.

Based on these recent figures, Tanner and Friedmann (1977) calculate that the daily intake for antimony is too negligible to assign a meaningful value.

Earlier reports of dietary intake of antimony indicated significant amounts assimilated daily. It is likely that part of this discrepancy is due to differences in analytical methodology. Schroeder (1970) calculated a value of somewhat less than 100 µg/day as the average dietary intake for man, while Murthy, et al. (1971) calculated a range of 0.25 to 1.28 mg/day for institutionalized children. In this study, a weighted average dietary antimony content of 0.36 mg/kg for these pediatric groups was determined.

Support for the recently reported very low antimony content of dietary classes in the United States (Tanner and Friedmann, 1977) is the survey of Clemente (1976), who reported the use of activation analysis in surveying food antimony content in Italian diets. A mean value of several micrograms Sb daily was obtained.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. An appropriate BCF can be used with data concerning food intake to calculate the amount of antimony which might be ingested from the consumption of fish and shellfish. An analysis (U.S. EPA, 1980) of data from a food survey was used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish is 6.5 g/day (Stephan, 1980).

A measured BCF of less than one was obtained for antimony using bluegills (U.S. EPA, 1978). For lack of other information, a value of 1.0 can be used as the weighted average bioconcentration

factor for antimony and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans.

Inhalation

Antimony is infrequently present in air at measurable levels. National Air Sampling Network data for 1966 showed possibly significant levels at only four urban stations (0.042 to 0.085 $\mu g/m^3$) and three nonurban facilities (0.001 to 0.002 $\mu g/m^3$) (Schroeder, 1970; Woolrich, 1973). It can be generally stated that urban ambient air levels of antimony are higher than nonurban levels, with the difference presumably reflecting the extent of greater fossil fuel combustion, municipal incineration, and auto emissions in urban areas.

Antimony is one of the elements which appears to concentrate in the smallest particles emitted in the fly ash from coal-fired power plants (Davison, et al. 1974). These small-diameter particles are both difficult to trap with conventional stack technology and are the size which penetrate the deepest in the pulmonary tract of man. While this suggests a relatively high level of respiratory absorption of at least part of the total airborne antimony, it is difficult to state that this poses any net hazard, given the overall low levels of total antimony.

Integrated Multimedia Exposure Estimates

In terms of the aggregate contribution of various exposure sources to the total daily intake of antimony by human populations in the United States, the total amount is quite small and even negligible relative to other environmental agents of concern, e.g., lead, mercury, or cadmium. For example, if one accepts the most

recently available data on dietary antimony intake (Tanner and Friedmann, 1977), then no appreciable additional antimony uptake via the diet would be expected. Also, essentially the same applies in regard to nonappreciable amounts of antimony being ingested via water consumption. This is consistent with the limited data of Clemente (1976) who, using fecal and urinary antimony levels, concluded that daily intakes of selected Italian populations were less than 2.0 µg/day. Also, an individual inhaling even the highest recorded ambient air level (0.085 $\mu g/m^3$) for an urban setting would be exposed to a total of 1.7 µg/day, assuming a daily inhalation rate of 20 cubic meters. It therefore appears that overall, multimedia antimony exposure levels for the general U.S. population are insignificant, or essentially negligible, in comparison to occupational exposure levels at which discrete clinical health effects have been observed.

PHARMACOKINETICS

Absorption

Data for the absorption of antimony from the respiratory tract, the gut, and skin are rather limited; as such, observed values may not broadly apply for all mammalian species, including man. Also, there is only very limited information on the effects of age or nutritional status in terms of increasing or decreasing the extent of antimony absorption. In addition, the kinetics of antimony uptake, distribution, and excretion are dependent on physical and chemical characteristics of the antimonials employed as well as the route of exposure and the species of experimental animals studied.

Antimony absorption from the respiratory tract is a function of particle size and solubility in the lung. The latter is dependent on the chemical form. This has been demonstrated experimentally by Felicetti, et al. (1974b) and Thomas, et al. (1973), who exposed experimental animals to aerosols generated from solutions containing ^{124}Sb-labeled antimony potassium tartrate. Prior to inhalation, the solutions were subjected to temperature treatment ranging from 100°C to 1,000°C. The higher heat treatment probably resulted in increasing degradation of the organic portion of the molecule and yielded different patterns of deposition and retention when inhaled. The lower temperature aerosols (100°C) were of a large particle size (1.3 um mass median aerodynamic diameter - MMAD). They were deposited to a large extent on the upper respiratory tract and were rapidly cleared via the mucociliary apparatus. However, the approximately 20 percent of these aerosols which were deposited in the lower respiratory tract were solubilized rapidly into the bloodstream. The higher temperature aerosols (500°C and 1,000°C) contained smaller particles (MMAD less than 1.0 μm) and were deposited deeper in the respiratory tract. These particles were relatively insoluble in the lung and were only slowly absorbed into the bloodstream. In a separate study (Felicetti, et al. 1974a) in which hamsters inhaled the 100°C aerosol, there was no difference in the pulmonary absorption of trivalent vs. pentavalent antimony material.

Data pertaining to the extent of gastrointestinal (GI) absorption of antimony in man and animals are sparse. According to one report (Felicetti, et al. 1974a), only 1 to 2 percent of antimony,

as either the trivalent or pentavalent forms, is absorbed from the GI tract of hamsters. It should be noted that these were the relatively insoluble oxides. It is likely that the water-soluble organic derivatives of antimony would be absorbed to a greater extent. Elinder and Friberg (1979) have noted that tartar emetic (potassium antimony tartrate) solution is about 15 percent absorbed in the GI tract of mice, based on earlier data of Waitz, et al. (1965).

Little information exists regarding the absorption of antimony through the skin. Gross, et al. (1955a), using antimony trioxide dust dispersed in a paste (25 mg), applied the oxide to the skin of rabbits and could see no sign of systemic effects. These workers did not, however, carry out any blood or tissue antimony determinations.

Few data exist regarding transplacental transfer of antimony in animals or man. Casals (1972) found no antimony in fetal tissues from rat dams exposed to pentavalent antimony intramuscularly for five doses, 125 or 250 Sb/kg, between days 8 and 14 of gestation. Similarly, James, et al. (1966) did not detect antimony in the tissues of lambs when ewes were daily given 2 mg/kg/day oral doses of antimony potassium tartrate from the first day of gestation for either 45 days or 155 days.

In humans, Belyaeva (1967) found antimony at detectable levels in placental tissue, amniotic fluids, and cord blood in pregnant women who worked in antimony smelters during pregnancy. It is difficult to evaluate the results of this study, since the analytical method employed may not permit specificity for just antimony.

Distribution

Blood is the main vehicle for transport of absorbed antimony to the various tissue compartments of the body. Several studies have shown that the relative partitioning of antimony between the erythrocytes and plasma is a function of element valency. That is, trivalent antimony is primarily lodged in red cells, while plasma carries the major fraction of the pentavalent form (Felicetti, et al. 1974a). Also, in a related *in vitro* study (Bahner, 1954) it was found that erythrocyte antimony is primarily bound to the globin moiety of hemoglobin. In this *in vitro* study, rodent erythrocytes were employed which may not be relevant for other species.

The levels attained and the clearance of antimony from blood depend upon the route of intake, the chemical and physical form of the antimonial used, and the specific parameters of exposure regimens employed in pertinent studies.

Levels of antimony in blood have been determined after inhalation of antimony aerosols by mice (Thomas, et al. 1973), dogs (Felicetti, et al. 1974b), and rats (Djuric, et al. 1962). In rats, unlike the other species, it was observed that inhalation leads to a persisting elevation of antimony in the blood. Djuric, et al. (1962) reported that animals inhaling antimony trichloride retained a blood concentration of 10 percent of the body burden 20 days beyond cessation of exposure.

Mice inhaling antimony aerosols generated at three temperatures (100°C, 500°C, and 1,000°C) and having corresponding mean aerodynamic diameters of 1.6, 0.7, and 0.3 μm at two days post-exposure showed the corresponding fractions per milliliter of blood

of the body burden to be 0.43, 1.2 and 1.0 percent, respectively (Thomas, et al. 1973).

Waitz, et al. (1965) used single oral doses of ^{124}Sb-labeled tartar emetic to assess the effect on blood levels in mice. Levels of antimony in blood up to 25 hours post-exposure were linearly related to dose while clearance from blood was both linearly and quadratically related with time. These same workers observed that oral exposure (8 mg Sb/kg) in monkeys led to average peak blood levels of 18 µg Sb/dl as observed 6 to 8 hours post-exposure.

Changes in blood antimony levels have also been followed after parenteral exposure of animals and humans. For example, a rapid decline in blood levels was observed in rats injected intravenously (i.v.) with 11 mg/kg trivalent antimony as ^{124}Sb-labeled tartar emetic, with the amount of decrease approximating 30 µg/dl after four hours. By comparison, the i.v. administration of 1.3 mg Sb/kg to three monkeys as reported by Waitz, et al. (1965) led to peak blood antimony levels of 125 to 190 µg Sb/dl at ca. 15 minutes post-injection, followed by a rapid decrease to 10 to 20 µg Sb/dl at 24 hours.

Casals (1972) studied the pharmacokinetic properties of a pentavalent antimony dixtran glycoside in mice, rats, and rabbits. Rabbits given this agent at a dosage of 14 mg Sb/kg intramuscularly had serum antimony levels of 6.5 mg Sb/dl Serum (65 µg Sb/ml) at five hours post-injection. After 72 hours, levels had decayed to ca. 2.0 mg Sb/dl (20 µg Sb/ml).

Abdalla and Saif (1962) injected ^{124}Sb-labeled Astiban, a trivalent antimonial, intramuscularly into human subjects at a dose

range of 1.4-2.1 mg Sb/kg and could not measure blood levels after single or repeated dosing. El-Bassouri, et al. (1963) similarly noted a rapid fall of blood antimony levels when pediatric patients with urinary schistosomiasis were given single injections of various trivalent antimonials (5 to 7 mg Sb/kg). Clearance of pentavalent antimony from blood in human subjects is also very rapid, with negligible amounts seen after 24 hours in subjects given the pentavalent antimonials intravenously at 2 to 3 mg Sb/kg dosing levels.

Data for normal blood antimony levels in man are limited. Sumino, et al. (1975), reporting on seven Japanese autopsy samples, found an average value of 1.3 µg Sb/dl (0.013 µg/ml) and a range of $<$ 0.01 to 0.06. Hirayama (1959a,b) obtained a normal upper limit value of 5.9 µg Sb/dl in whole blood for healthy Japanese residing in an urban area. Levels were higher for men than for women.

Under conditions of occupational exposure, blood antimony levels are elevated. Belyaeva (1967) reported a mean blood level of 5.3 $\pm$ 0.6 µg/dl.

The tissue distributions of antimony under conditions of experimental and environmental exposure have been reported for both laboratory animals and samplings of human autopsy material.

Kostic, et al. (1977) employed instrumental neutron activation analysis to study the antimony content of various organs of normal rats (not exposed to antimony experimentally). Expressed as both µg Sb wet weight and total organ content, respectively, the corresponding mean values were: brain, 0.4 and 0.7 µg; lung, 0.6 and 1.0 µg; heart, 0.47 and 0.33 µg; kidney, 0.46 and 0.89 µg; spleen, 1.14 and 0.61 µg; and liver, 1.31 and 10.40 µg. From these tissue pro-

files, it appears that low ambient antimony exposu.. leads to highest levels in liver, followed by spleen and lung.

The tissue distributions of antimony in exposed experimental animals are tabulated in Table 1 according to the type and level of exposure, the animal model employed, and the relative distribution of antimony among different tissues as observed in various studies.

From Table 1, it appears that tissue distribution of antimony is a function of valency state when inhaled, with levels of trivalent antimony increasing more rapidly in liver than the pentavalent form, while skeletal uptake is greater with the pentavalent antimonial (Felicetti, et al. 1974a).

Antimonial aerosols with different physicochemical characteristics are absorbed from the lung at different rates. This is illustrated by the fact that aerosols generated from antimony potassium tartrate solutions are more soluble in the lung when generated at low (100^{o}C) as opposed to high temperature (500^{o}C or 1,000^{o}C) (Thomas, et al. 1973; Felicetti, et al. 1974b). The higher temperatures may have resulted in formation of oxides. With the soluble aerosols, inhaled by dogs, radioactive antimony accumulated in lung, thyroid, liver, and pelt, with the thyroid gland having the greatest concentration. The latter results are consistent with the findings of Ness, et al. (1947), who reported that the thyroid was a target organ for antimony accumulation in dogs when organic antimonial compounds were injected i.v.

Parenteral administration of antimonials generally tends to show a greater accumulation in the kidneys, followed by liver, and mineral tissue (Molakhia and Smith, 1969; Waitz, et al. 1965).

TABLE 1

Tissue Distributions of Antimonials in Different Species Under Various Exposure Conditions

Route of Exposure Species	Dosing (Antimonial)	Tissue Distribution	Reference
ORAL EXPOSURE			
Normal mice	Oral (^{124}Sb-labeled tartar emetic): Single dose, 16 mg Sb/kg and greater	Liver antimony levels increase linearly with dose and quadratically with time	Waitz, et al. 1965
Mice infected with S. mansoni	Oral (^{124}Sb-labeled tartar emetic): 16 mg/kg daily for 2, 4, 6, 8 or 10 days	Liver antimony levels were uniform from day to day with little accumulation	Waitz, et al. 1965
INHALATION EXPOSURE			
Mice	Inhalation (^{124}Sb aerosols): ^{124}Sb aerosols generated at 100°C, 500°C, and 1,000°C	Aerosols generated at 100°C had ca. one-tenth less antimony in lung compared to 500°C and 1,000°C. 100°C aerosol showed 85% of body burden lodged in skeleton by 52 days, much more than for aerosols generated at 500° and 1,000°	Thomas, et al. 1973
Dogs	Inhalation (^{124}Sb aerosols): generated at 100°C, 500°C, and 1,000°C	^{124}Sb levels were highest in lung, thyroid, liver and pelt, with thyroid having greatest accumulation for 100°C aerosol and lung the greatest level for 500° and 1,000° aerosols	Felicetti, et al. 1974b
Hamsters	Inhalation (trivalent and pentavalent aerosols from ^{124}Sb-tartrate): aerosols generated at 100°C, 1.6 μm mean aerodyn. diameter	Highest levels for both valency forms were seen in liver, skeleton and pelt, with relatively greater amount of trivalent antimony in liver than of pentavalent form by day 5 post-exposure. Skeletal values greater with pentavalent form	Felicetti, et al. 1974a

TABLE 1 (continued)

Route of Exposure Species	Dosing (Antimonial)	Tissue Distribution	Reference
SYSTEMIC INJECTIONS			
Mice infected with S. mansoni	Intraperitoneally (tartar emetic or Astiban-sodium antimony dimercapto-succinate): 5 mg/kg, tartar emetic; 7.5 mg/kg Astiban	Both antimonials led to highest uptakes in liver and kidney by 48 hr. Over 2-15 days, levels in mineral tissue (bone and teeth) began to exceed levels in other tissues. Pelt levels were uniformly high while brain, thyroid and male reproductive organs showed least uptake	Molakhia and Smith, 1969
Rats	Intravenous (^{124}Sb tartar emetic): 11 mg/kg, single injection: 6 rat pairs at 0.5, 2, 4, 8, 24 and 72 hr.	Kidney antimony levels were higher than liver antimony levels at all time points	Waitz, et al. 1965
Rats	Intravenous (^{122}SbOCl or $Na^{122}SbO_2$): sacrifice at 1 and 4 hours	Highest antimony levels were seen in kidneys, bone and spleen: kidneys had 3.9% of the dose/g with ^{122}SbOCl and 1.31% of the dose/g with $Na^{122}SbO_2$	Matthews and Molinaro, 1963
Mice	Intraperitoneally (^{124}Sb tartar emetic): 1) pre-treated group with 35 mg Sb/kg followed by labeled 35 mg Sb/kg dose; 2) control group treated with labeled 35 mg Sb/kg dose	Liver levels of antimony were equal for pre-treatment and control groups. Heart, spleen and kidney levels were lower in pretreatment group	Girgis, et al. 1965
Dog	Intravenous organic antimonial compounds	Thyroid hypothesized as antimony target organ based on high Sb uptake	Ness, et al. 1947
Human	Intravenous (^{124}Sb-Astiban-sodium antimony dimercapto succinate): single 100 mg dose, followed for 23 days	Largest antimony uptake was seen in liver, followed by the thyroid and the heart	Abdalla and Saif, 1962

In the study of Abdalla and Saif (1962), an Egyptian male had highest antimony uptake in liver, thyroid, and heart when given a single injected dose of labeled Astiban (100 mg).

Tissue distributions in man have mainly involved the study of autopsy material. Based on the detailed study of Sumino, et al. (1975), which used human tissue samples from Hyogo Prefecture in central Japan, all organs had antimony levels of less than 0.1 ppm wet weight, with a mean total body burden of about 1.0 mg. The skin had the highest mean level, 0.096 $\pm$ 0.10 ppm, followed by the adrenal gland, 0.073 $\pm$ 0.14 and the lung, 0.062 $\pm$ 0.056 ppm. Liver, spleen, and heart levels were lower.

Lievens, et al. (1977) employed radiochemical neutron activation analysis to measure a number of trace elements, including antimony, in segments of normal liver from five autopsies of residents of Belgium. A mean value of 0.011 µg/g wet weight was obtained, with a range of 0.003 to 0.020. This is within an order of magnitude of the mean liver level, 0.023 µg Sb/g wet weight, obtained by Sumino, et al. (1975).

Specific human tissue analyses for antimony have also been reported. For example, in one study, lung tissues from adults 40 to 70 years of age in Glasgow, Scotland, were analyzed for antimony content using neutron activation analysis (Molakhia and Smith, 1967). A mean value of 0.095 ($\pm$ 0.105) µg/g wet tissue was obtained, with a range of 0.007 to 0.452 µg. The distribution of antimony within the lungs analyzed was such as to suggest the element arose from airborne dust. In a related study, Kennedy (1966) measured diseased and normal lung tissue from 24 subjects for anti-

mony content, obtaining a range of 0.005 to 0.87 µg/g wet tissue. Lungs with pulmonary lesions did not appear to be different in antimony content than control samples.

Brune, et al. (1980), in their study of elements in kidney, liver, and lung tissue from autopsy samples of retired workers who were employed in a smelter and refinery, noted that the median level of antimony in lungs of former smelter workers were significantly greater than controls. The median antimony levels in lung tissue of one worker group (2-19 years between retirement and death) was 0.32 ppm and a range of 0.023-2.6 (N=23) versus control values of 0.029 ppm, range 0.011-0.054 (N=9). Since other data from nonoccupational subjects suggests little antimony accumulation in the lungs, smelter workers may inhale a very insoluble form of the element, possibly the sulfide.

Using neutron activation analysis, Hogenfeldt, et al. (1977) measured antimony and other trace elements in human decidua obtained from Swedish subjects during the 12th to the 18th week of pregnancy. In 14 samples, levels of antimony had a geometric mean value of 0.024 µg/g dry tissue and a range of 0.02 to 0.03. The mean antimony level in decidua was considerably less than that in endometrium in either proliferative or secretory phase.

In a study of human dental enamel, Rasmussen (1974) determined the antimony content for 12 Danish subjects using neutron activation analysis and found a range of $<$ 0.001 to 0.006 µg Sb/g enamel. The range of levels in this study is less than that found by Nixon, et al. (1967), who reported 0.005 to 0.665 µg/g, also using activation techniques. The difference may reflect more complicated sam-

ple manipulations in the latter study, which would have increased the risk of contamination.

The antimony content of cardiac tissue from autopsies of 20 victims of accidental death was determined by Wester (1965), who obtained a median concentration of 0.015 ug/g wet tissue using activation analyses, with a range of 0.001-0.004. No differences were seen with sex or age.

Levels of antimony in human brain are relatively low, consistent with a low neurotoxicity potential for this agent as seen from its therapeutic use. Hock, et al. (1975), analyzing eight regions of six brains, found a cerebral cortex value range of 0.025 to 1.71 ug/g dried tissue.

Based on the foregoing discussion, it appears that antimony accumulates most highly in selected soft tissues, e.g., kidney, liver, thyroid, certain other endocrine organs, and, to some extent, the heart.

According to the International Commission on Radiological Protection (ICRP, 1960), antimony is calculated to have a total human body half-time of 38 days and tissue half-times of: liver, 38 days; thyroid, 4 days; lungs and bone, 100 days. The accuracy of such estimates by the ICRP, however, has been questioned.

Abdalla and Saif (1962) found the half-times in man of parenterally administered antimony as chemotherapeutic agents to vary with the intramuscular and intravenous routes. For intramuscular injection, half of the total dose was excreted by 30 days while with i.v. treatment, half of the dose could not be recovered by 34 days.

From the whole-body data of Waitz, et al. (1965), parenterally administered ^{124}Sb-tartar emetic in rats had a half-time of less than 24 hours while Thomas, et al. (1973) showed that ^{124}Sb-labeled antimony aerosols inhaled by mice gave whole-body data that included a half-time of 29 days for the more rapidly cleared 100°C aerosols versus 39 days for the aerosols generated at higher temperatures.

Using beagle dogs and ^{124}Sb-labeled antimony aerosols generated at 100°, 500°, and 1,000°C, Felicetti, et al. (1974b) calculated corresponding long-term biological half-times of 100, 36, and 45 days, respectively. These authors also determined that with the same aerosol model and using hamsters, both tri- and pentavalent antimony body clearance had a fast component of several days and a slower clearance component of 16 days. In this study, lung solubility for the 500° and 1,000°C aerosols is a key factor.

With regard to tissue accumulation, particularly in man, limited data suggest that both soft and mineral tissue show little tendency to accumulate in unexposed populations, although one recent report (Brune, et al. 1980) suggests antimony accumulation occurred in smelter workers who had been retired from work activity for at least several years. Even though bone antimony tends to have a longer half-time than antimony in body soft tissue, this is considerably less than for certain other toxic heavy metals.

Metabolism

Absorption of antimony in man and animals is mainly via the respiratory and gastrointestinal tracts, the extent of absorption depending on factors such as solubility, particle size, and chemi-

cal forms. Absorption via the GI tract is on the order of several percent with antimony trioxide, a relatively insoluble compound, and presumably would be much greater with soluble antimonials.

Blood is the main carrier for antimony, the extent of partition between blood compartments depending on the valence state of the element and the animal species studied. The rodent exclusively tends to concentrate trivalent antimony for long periods in the erythrocyte. Whatever the species, it can generally be said that pentavalent antimony is borne by plasma and trivalent antimony in the erythrocyte. Clearance from blood to tissues of antimony is relatively rapid; this is especially true in the case of parenteral administration and the use of pentavalent antimony.

The tissue distribution and subsequent excretion of antimony is a function of both route of administration and valence state.

Trivalent antimony aerosols lead to the highest levels in the lungs, skeleton, liver, pelt, and thyroid while pentavalent form aerosols show a similar distribution with the exception of lower levels in liver.

Parenteral administration to animals shows trivalent antimony accumulating in the liver and kidney as well as in pelt and thyroid.

In man, nonoccupational or nontherapeutic exposure shows very low antimony levels in various tissues with limited evidence of accumulation in smelter workers. Chemotherapeutic use leads to highest accumulation in liver, thyroid, and heart for trivalent antimony.

The half-time of antimony in man and animals is a function of route of exposure and oxidation state. The rat appears to be unique in demonstrating a long biological half-time owing to antimony accumulation in the erythrocyte. In other species, including man, moderate half-times on the order of days have been demonstrated. While most soft tissues do not appear to accumulate antimony, the skin does show accumulation owing to its high content of sulfhydryl groups. With respect to excretion, injection of trivalent antimony leads to mainly urinary excretion in guinea pigs, dogs, and humans and mainly fecal clearance in hamsters, mice, and rats.

Owing to its higher levels in plasma, pentavalent antimony is mainly excreted via the kidney in most species .

Unexposed humans excrete less than 1.0 µg antimony daily via urine, while occupational or clinical exposure may result in markedly increased amounts.

Excretion

The kinetics of antimony excretion appear to be a function of the animal species, route of intake of the element, and the chemical form (oxidation state) of antimony.

Parenteral administration of trivalent antimonials leads to rapid urinary excretion in guinea pigs, dogs, and humans (Otto and Maren, 1950; Abdalla and Saif, 1962), while fecal clearance is more important with hamsters, mice, and rats.

Animals inhaling pentavalent antimony aerosols tend to excrete the element by both the GI and renal tracts, reflecting entry of some of the inhaled material into the GI tract by mucociliary movement and swallowing.

Generally, pentavalent antimony is more rapidly excreted in the urine than is the trivalent form, reflecting the attainment of higher plasma levels by the pentavalent form.

Little information on daily urinary output of antimony in man is available. Clemente (1976) used neutron activation analysis to determine that $<$0.3 µg was excreted daily in an unexposed Italian population. Under conditions of occupational exposure, urinary excretion is elevated but highly variable from subject to subject (Cooper, et al. 1968). Similarly, chemotherapeutic treatment of patients with antimony parasiticides leads to high levels of excretion. These agents are fully soluble and given at comparatively high doses. Abdalla and Saif (1962) have measured 24-hour levels of antimony of ca. 20 to 40 µg/dl after parenteral administration of 75 to 125 mg Astiban®.

As internal indices of exposure, usefulness of blood and/or urine antimony levels are of undetermined value. Generally, urinary levels of antimony increase under conditions of occupational or chemotherapeutic exposure and it appears that such values would reflect the intensity of ongoing exposure. Similarly, blood levels rapidly rise and fall with onset and removal of exposure.

EFFECTS

Only a relatively limited data base exists in regard to the study of biological and pathological effects of antimony in experimental animals and humans. Such effects include various cellular and subcellular effects, as well as toxic actions manifested at organ system levels. The latter type of systemic toxicity includes damage to the lungs, heart, liver, spleen, and endocrine organs, as well as toxic effects exerted on reproduction and development.

Acute, Subacute, and Chronic Toxicity

Acute toxicity tests with antimony and antimonial compounds were carried out by Bradley and Fredrick (1941). The observed LD_{50} obtained after either oral or intraperitoneal (i.p.) administration are indicated in Table 2. As discussed later, responses to the LD_{50} doses included labored breathing, general weakness, and other signs of cardiovascular insufficiency leading to death among many animals within a few days after exposure. It should be noted that, of the antimony compounds tested, the trifluoride is mainly of interest in regard to laboratory or experimental use, in contrast to most of the other agents being encountered in industrial settings.

Levina and Chekunova (1965) also studied LD_{50}s for antimony compounds, using subcutaneous (s.c.) and intratracheal administrations in mice and rats, respectively. They obtained an LD_{50} of 50 mg Sb/kg for antimony trifluoride with single s.c. injections in mice, whereas 50 mg Sb/kg was found to be without obvious toxic effect during a 10- to 30-day observation period when antimony trioxide, trisulfide, or pentasulfide were administered subcutaneously. Subcutaneous injection of antimony trioxide at a dose of 500 mg/kg, however, was universally (100 percent) fatal. Single intratracheal doses of 2.5 to 20 mg of antimony trifluoride administered to rats were also 100 percent fatal, whereas lower doses of 1.0 to 1.5 mg were survived with minimum toxic effects being seen. Doses of antimony trioxide and trisulfide were tolerated much better, with 20 mg of those compounds producing temporary weight loss as the only sign of toxicity.

TABLE 2

LD_{50} of Antimony and Compounds*

Compound	Species	Route	LD_{50} mg/kg
Tartar emetic	Rat	oral	300
Tartar emetic	Rat	i.p.	11
Antimony trifluoride	Mouse	oral	804
Antimony	Rat	i.p.	100
Antimony	Guinea pig	i.p.	150
Antimony trisulfide	Rat	i.p.	1,000
Antimony pentasulfide	Rat	i.p.	1,500
Antimony trioxide	Rat	i.p.	2,250
Antimony pentoxide	Rat	i.p.	4,000

*As determined by Bradley and Fredrick, 1941

This section discusses certain biochemical and subcellular aspects of antimony toxicity per se, where studied as such. Other biochemical and cellular effects occurring as part of the systemic toxicity of antimony are noted later - under sections on specific organ systems.

Effects of antimony at the biochemical level are little understood at present, and the available information is correspondingly limited. Unlike many of the toxic heavy metals, which are cationic in character and directly interact with ligating groups such as the sulfhydryl, amino, and carboxyl moieties of macromolecules and their constituent units to form biocoordination complexes, antimony probably resembles arsenic in the nature of its bonding. Trivalent antimony forms covalent bonds with sulfhydryl groups and pentavalent antimony, like pentavalent arsenic, competes with phosphate to form ester linkages.

Evidence for this assumed overlap of chemical behavior with arsenic is mainly indirect. Tissues high in sulfhydryl groups, such as skin, tend to show pronounced accumulation of antimony, as noted above in the metabolism section. Further, in the rodent, the red cell accumulation of trivalent antimony parallels that seen with arsenic [National Academy of Sciences (NAS), 1977].

In vitro studies directed to antimony's effects on enzymes and enzyme systems are very limited. In a study of homogenate of adult S. mansoni worms, Mansour and Bueding (1954) observed an effect of stibophen or tartar emetic on phosphofructokinase, as measured by inhibition in the formation of fructose-1,6-diphosphate from fructose-6-phosphate. No other glycolytic enzymes appeared to be anti-

mony-sensitive even at high concentrations, nor was phosphofructokinase from another source (rat brain preparations) as sensitive to antimony. Pentavalent antimony was without effect on any enzyme studied.

Incubation of rat liver mitochondria for a brief period with sodium antimony gluconate, a trivalent antimonial, showed a concentration-dependent effect on oxidative phosphorylation, presumably localized at the NADH-oxidase portion of the electron-transfer chain (Campello, et al. 1970). The minimal concentration necessary for this observation was ca. 4×10^{-3} M Sb.

In vivo effects of antimonials on enzymatic activity have been sporadically noted in the literature. Parenteral administration of antimony trioxide (163 mg/kg) in rats, for instance, led to increased activity of cholinesterase in myocardium but decreased monoamine oxidase activity in brain and liver (Minkina, et al. 1973).

Certain other disturbances of biochemistry have also been reported for antimonials. In a study of carbohydrate metabolism, Schroeder, et al. (1970) found that lifetime exposures of rats to low levels of antimony resulted in decreased serum glucose levels in nonfasting animals. Other biochemical changes reported include increased glutathione in the blood of antimony-exposed animals (Maeda, 1934) and increased nonprotein nitrogen and hemoglobin content in blood of rabbits exposed to tartar emetic (Maeda, 1934; Pribyl, 1944).

Studies on the uptake and subcellular distribution of antimonials have been reported by Smith (1969) using in vitro tech-

niques. Mouse liver slices incubated with ^{124}Sb-labeled tartar emetic showed a marked antimony accumulation with accompanying cellular necrosis. Total uptake was up to 18-fold greater than measured in healthy tissue. Subcellular fractionation indicated that about two-thirds of the label was in the particulate matter, primarily the microsomal fraction. It is not clear, however, whether the cellular necrosis observed was induced by the antimony per se or strong beta emissions of the ^{124}Sb isotope. Nor is it clear as to whether the high uptake of the labeled compound occurred secondarily to the cellular damage.

Mutagenicity and Carcinogenicity

The few chronic feeding studies that have investigated possible antimony carcinogenicity in animals have produced negative results (Kanisawa and Schroeder, 1969; Schroeder, et al. 1970), with no increases in tumorigenesis being observed at antimony concentrations of 5 ppm either administered via the diet or drinking water. While the results were negative, the acceptance of this compound as a noncarcinogen is precluded by the lack of additional exposure levels, including higher doses.

Several studies have reported mutagenic potential for various antimony compounds (Kanematsu and Kada, 1978; Flassel, 1977; Paton and Allison, 1972). In their examination of 100 metal compounds by the rec-assay procedure, a test which assesses the differential inhibition of cellular growth of a recombinant-deficient strain of B. subtilis versus the wild strain, three antimonials - antimony trioxide, antimony trichloride, and antimony pentachloride - were found to be positive. Paton and Allison (1972) observed toxic

effects of tartar emetic on human leukocytes in culture at levels as low as 10^{-8} M as measured by significant reduction in mitotic index as well as an increase in the number of chromatid breaks in chromosomes.

Respiratory System Effects

As discussed later, certain types of respiratory illnesses, including pneumoconiosis, have been observed with human exposures to antimony via inhalation. Some efforts, however limited, have been made to study analogous types of respiratory toxicity in experimental animal models under controlled laboratory conditions.

In one of the earliest studies, Dernehl, et al. (1945) observed respiratory effects in guinea pigs exposed to antimony trioxide via inhalation. Exposures to concentrations averaging 45.4 mg/m^3 for 2 hr/day, 7 days/week for three weeks and 3 hr/day thereafter yielded marked respiratory pathology. This included widespread pneumonitis in animals estimated as retaining from 13 to 424 mg of antimony and scattered subpleural hemorrhages seen in all animals retaining 50 mg or more of the antimony compound. The very wide range of estimated effective or retained doses associated with the observed health effects are notable.

In another study (Gross, et al. 1952) lipoid pneumonia was induced in 50 rats exposed to antimony trioxide at 100 to 125 mg/m^3 (mean particle size = 0.5 μm) for 25 hr/week for a 14.5 month period. The lung pathology induced by antimony was characterized by: (1) cellular proliferation, swelling, and desquamation of alveolar lining cells; (2) fatty degeneration, necrosis, and rupture of alveolar macrophages; and (3) pulmonary fibrosis.

In a second study by Gross, et al. (1955b), a similar inhalation exposure regimen was employed for exposure of 50 rats, while 20 rabbits were exposed at 89 mg/m^3 for 25 hr/week for 10 months. A relatively high mortality rate was observed: 18 percent for the rats and 85 percent for the rabbits, mainly attributable to antimony-induced pneumonia. Histological findings were similar to those observed in the previous Gross, et al. (1952) study except for somewhat less widespread fibrosis in the rat lungs and more pronounced interstitial pneumonia in the rabbits. Again, no lymph node fibrosis was observed in either species, even though some antimony deposits were seen in lymph nodes of each.

Subsequent to the Gross, et al. (1952, 1955b) reports, only two other studies (Levina and Chekunova, 1965; Cooper, et al. 1968) provide much additional information regarding antimony effects on the lungs. In the Levina and Chekunova (1965) study, for example, intratracheal injections of 20 mg of antimony trioxide, trisulfide, or pentasulfide in rats resulted in immediate reductions in body weights for several days and, upon sacrifice a month post-injection, lung histopathology findings indicating signs of macrophage reaction, accumulation of lymphoid elements around blood vessels and bronchi, and accumulations of epitheloid cells in other areas.

By comparison to the above results, much more severe effects were observed by Levina and Chekunova (1965) with intratracheal injections of a halogenated antimonial, i.e., antimony trifluoride. That is, single doses of 2.5 to 20 mg of the trifluoride compound produced 100 percent mortality in exposed rats, with death occurring due to asphyxia following the onset of labored breathing and

convulsions within minutes after the injections. Acute serous or serohemorrhagic edema, causing a 3-fold increase in lung weight, was evident upon post-mortem inspection. In rats surviving lower exposures (1.0 to 1.5 mg) to the trifluoride compound, signs of pulmonary edema were observed at sacrifice a month after exposure although lung weights were normal then.

The 1968 studies by Cooper, et al. investigated the effects on 10 male and 10 female rats of exposure to powdered antimony ore or antimony trioxide. Those compounds were presented in aerosol form at a concentration of 1,700 mg/m^3 during 1-hour exposure sessions repeated once every two months for up to one year, with representative subjects exposed to each compound being sacrificed at intervals during the study period. Immediately after exposure to the ore, but not the trioxide, transitory generalized pulmonary congestion with some edema occurred, probably due to an acute chemical pneumonitis. Otherwise, the same types of effects were seen with exposure to either the ore or the trioxide. That is, at two months after exposure to each compound, macrophages with massive accumulations of phagocytized material were observed within alveolar spaces or among cells of the septa, at times forming focalized deposits within many areas of the lung. Further exposures resulted in increasingly more extensive focalized deposits, with the phagocytic response still being evident at the largest time points assessed for each compound, i.e., 311 and 366 days after exposure for the trioxide and ore compounds, respectively.

The above animal toxicology studies provide consistent evidence for marked respiratory effects being exerted by antimony com-

pounds following inhalation exposure. The studies, however, have been quite limited in that none have approached two crucial issues: (1) assessment of antimony-induced alterations in pulmonary function; or (2) systematic definition of dose-effect/dose-response relationships for either functional or histopathological changes associated with antimony exposure.

Given the dearth of information bearing on the latter point, it is not now possible to estimate, with any certainty, the no-effect level for respiratory problems associated with exposure to antimony. About all that can be said is that this no-effect level is likely higher for the trioxide compound than for antimony trifluoride. Also of considerable importance is the fact that many of the pathologic respiratory effects observed in the above animal studies do not always comport well with observations in cases of human exposure to antimony compounds. This is especially notable in regard to the lack of evidence in humans of the extensive pulmonary fibrosis seen in rodents following inhalation exposure to antimony. On the other hand, there do exist reports of observations indicating increased phagocytic acitvity and proliferation of lung macrophages in both animals (Levina and Chekunova, 1965; Cooper, et al. 1968) and humans (McCallum, 1967) following inhalation exposure to antimony compounds; the increased macrophage presence and phagocytosis activity, however, is of uncertain pathological significance, occurring as it does in a nonspecific fashion in response to inhalation of dusts or particulate matter. Probably of more consequence are the observations in the above animal toxicology studies of lipoid and interstitial pneumonia following inhalation exposures.

Cardiovascular System Effects

Consistent with observations in humans, several animal toxicology studies have yielded data documenting marked effects of antimony compounds on the heart. For example, myocardial damage has been reported following exposures to antimony compounds via inhalation (Brieger, et al. 1954), acute injection, and oral ingestion (Bradley and Fredrick, 1941).

As indicated earlier (Table 2), Bradley and Fredrick (1941) determined LD_{50}s for various antimony compounds administered to rats, mice, or guinea pigs orally or via direct i.p. injection. Animals dying within a few days after injection showed labored breathing, body weight loss, general weakness, and other evidence of myocardial insufficiency; post-mortem examination revealed myocardial congestion with engorgement of cardiac blood vessels and dilation of the right side of the heart. Histopathological evidence of myocardial damage was also observed in hearts of animals surviving the LD_{50} tests, including marked variations in myocardial fiber staining seen with most all of the antimony compounds and a distinct increase in connective and fibrous tissues of the myocardium in the antimony potassium tartrate treated animals.

Bradley and Fredrick (1941) also fed animals antimony potassium tartrate and antimony metal in daily doses that ranged up to 100 mg/kg and 1,000 mg/kg, respectively, for up to one year. Significant myocardial effects were reported to have occurred at both the 100 and 1,000 mg/kg dose levels; the potassium tartrate compound, for example, consistently produced myocardial damage, indexed by observed proliferation of connective and fibrous tissues of the

myocardium and alterations in staining of myocardial fibers similar to those observed in animals surviving the acute injection tests. Ambiguous statements regarding results obtained at lower exposures make it impossible to determine if any "no-effect" level was ascertained for the myocardial effects seen at the 100 or 1,000 mg/kg dose levels.

Additional evidence for antimony-induced myocardial effects was obtained in a series of inhalation studies conducted by Brieger, et al. (1954). Rats, rabbits, and dogs were exposed to dusts with concentrations of antimony trisulfide ranging from 3.1 to 5.6 mg/m^3 for 7 hr/day, 5 days/week for at least six weeks. Not only was parenchymatous degeneration of the myocardium observed in the rats and rabbits, but also, consistent functional deficits were seen as indexed by ECG alterations, e.g., flattened T-wave patterns. The inhaled antimony particles were found to be generally < 2 µm in size.

The particular types of changes observed in the above animal experiments are consistent with myocardial effects seen in humans exposed to antimony compounds. Altered T-wave ECG patterns, for example, have also been observed in humans occupationally exposed to antimony trisulfide (Brieger, et al. 1954; Klucik and Ulrich, 1960) at levels comparable to those employed in the above animal experiments, e.g., at 3.0 to 5.6 mg/m^3 (Brieger, et al. 1954). Unfortunately, no systematic evaluation exists for dose-effect/dose-response relationships for antimony-induced myocardial effects in experimental animal models, making it impossible at this time to suggest accurate estimates of "no-effect" levels for the myocardial damage.

Blood Effects

Only very limited information has been generated in regard to antimony effects on blood elements in experimental animals. Bradley and Fredrick (1941), for example, reported normal blood parameters for rats exposed in their LD_{50} studies, except for distinctly increased eosinophilia after LD_{50} doses of all of the antimony compounds tested (see Table 2).

In the only other study providing information, Dernehl, et al. (1945) observed blood changes in guinea pigs exposed by inhalation to doses of antimony trioxide that averaged 45 mg/m^3; the exposures employed were stated to be for two hours daily for three weeks and then for three hours daily for several weeks. The blood changes observed included decreased white blood cell counts, decreased polymorphonuclear leukocytes, and increased lymphocyte counts, while red blood cell counts and hemoglobin levels were normal.

Liver, Kidney, Spleen, and Adrenal Effects

Scattered information exists regarding antimony effects on certain other internal organs, e.g., the liver, kidneys, spleen, and adrenal glands. Bradley and Fredrick (1941), for example, observed liver effects in their studies on i.p. LD_{50} for different antimony compounds. Such liver effects included periportal congestion, increased blood pigmentation, increased numbers of plasma cells, and mild hepatotoxemia indexed by functional hypertrophy of hepatic cells. As for spleen effects, no changes were seen with antimony oxides, but slight congestion and diffuse hyperplasia was seen after exposure to antimony metal or tartrate. In the kidneys of animals receiving the metal or tartrate, glomerular congestion

was observed with coagulated material being present in kidney tubules.

Dernehl, et al. (1945) later observed fatty degeneration of the liver in rats exposed to antimony trioxide via inhalation of which at least 77 mg of antimony was retained in their lungs. Abnormal spleen pathology was also detected and included such changes as hyperplasia of lymph follicles, decreased numbers of polymorphonuclear leukocytes, abnormal amounts of blood pigment, and large numbers of antimony-laden phagocytes.

Liver and kidney changes were also observed by Levina and Chekunova (1965) after 25 s.c. doses of 15 mg/kg of antimony trifluoride administered to rats over a 1-month period. In the liver, areas of edema, fatty infiltration and cloudy swelling were observed. Somewhat more marked degenerative changes were seen in the kidneys, e.g., swelling of epithelial cells lining the convoluted tubules, nuclear pyknosis and desquamation of epithelium, hemorrhages, protein masses in tubular lumina, and occasional shrunken glomeruli.

In regard to effects on the adrenals, one study (Minkina, et al. 1973) evaluated the effects of antimony trioxide injections administered to rats subcutaneously five times per week for three months, for a total dosage of 165 mg. After 20 injections, a broadening of the cortical layers of the adrenals was observed due to growth of the fascicular and reticular zones; this was accompanied by increased nuclear diameters and monoamine oxidase activity taken by the authors to be indicative of increased adrenocortical functional activity.

Reproduction, Development, and Longevity

One of the few pertinent studies on reproductive effects of antimony is that reported by Belyaeva (1967) in which female rats were exposed either to antimony dust via a single i.p. injection of 50 mg/kg or to antimony trioxide dust for 4 hr/day for 1.5 to 2 months at a concentration of 250 mg/m^3. The females were mated in estrous three to five days after the acute injection, whereas the inhalation exposure was continued throughout gestation following mating. Of the 30 acutely-treated dams, 15 failed to conceive compared to only one failure among control dams. Of the 24 chronically exposed females, eight failed to conceive versus no failures among 10 control females. In each case, both acutely and chronically exposed dams produced fewer offspring than the unexposed control animals. Histological examinations of females from both exposure groups and control animals revealed uterine and ovarian changes likely to interfere with maturation and development of egg cells. For instance, ovarian follicles of exposed animals often lacked ova or contained misshapen ova or ovarian cortical hyperemia; or cysts were present. At times, metaplasia of the uterus or fallopian tubes was also seen. The most marked histopathologic changes were found in the animals receiving i.p. injections of antimony metal.

In another pertinent report on antimony and reproduction, Casals (1972) observed no effects, i.e., no fetal abnormalities, following administration of a solution of antimony dextran glycoside containing 125 or 250 mg Sb/kg to pregnant rats on five days between days 8 and 14 of gestation. It is interesting that no

effects on fetal development were observed in the Casals study at much higher exposure levels employed than those used in the Belyaeva (1967) study, where a significant impact was reported on conception and the number of offspring born to antimony-exposed dams.

In addition to the above studies on reproduction, a few investigations provide information on the potential effects of oral exposures to antimony on postnatal growth, development, and longevity. For example, Gross, et al. (1955a) compared effects of feeding two groups of 10 rats each a synthetic diet containing 2 percent antimony trioxide with results obtained for 20 control animals fed the same diet without antimony for a comparable 8-month period. The antimony-exposed animals exhibited a slower rate of growth over the 8-month period, reaching a final average weight of 300 g versus 350 g for the control rats. No other effects were detected upon microscopic examination of various tissues despite notable accumulations of antimony in blood and soft tissues of exposed animals.

Schroeder, et al. (1970) also reported on the effects of chronic oral exposure to antimony but at a much lower exposure level of 5 ppm (as the metal) administered via drinking water adulteration with potassium antimony tartrate. The 5 ppm exposure level was reported to have negligible effects on growth or mature weight of antimony-exposed animals, but the life spans of such animals were shortened significantly; that is, males survived 106 days and females 107 days less than controls at median lifespans. Also, nonfasting glucose levels were significantly lower than fasting glucose levels for male rats exposed to antimony, and significant

variations in serum cholesterol from control levels were observed for both male and female rats exposed to antimony. The effects on longevity, suggestive of toxicity in rats being induced by oral exposure to 5 ppm of antimony, were also observed for female mice chronically exposed to 5 ppm of antimony in their drinking water in another study (Kanisawa and Schroeder, 1969).

Skin and Eye Effects

A series of experiments conducted by Gross, et al. (1955a) investigated the irritant effects of antimony trioxide in the skin and eyes of rabbits and rats. Antimony trioxide (mean particle size of 1.3 μm), with up to 0.2 percent arsenic as a contaminant, was administered in 1 mg quantities in 1 ml of an aqueous suspension directly into one eye of each animal. No signs of irritative effects on the conjunctiva or cornea were evident at one, two, or seven days post-injection.

In cutaneous toxicity tests, antimony trioxide dust (2.6 g) was mixed into an aqueous methyl cellulose paste and was applied to shaved areas of the torso. After one week, during which the treated area was covered, no local skin reactions were observed on or around the treated areas. Also, no signs of systemic toxicity were observed, suggesting that dermal absorption of antimony had probably not taken place - although no measurements of antimony in blood or in excreta were carried out to confirm that suggestion.

Summary of Animal Toxicology

Based on the above studies, it is clear that certain respiratory effects are consistently induced in rodents after inhalation exposures to antimony; this includes increased macrophage prolifer-

ation and activity, pulmonary fibrosis, and certain types of pneumonia. Probably of even greater significance for present purposes are marked myocardial functional and histopathological effects consistently demonstrated to occur as the result of either inhalation or oral ingestion exposure to antimony. Unfortunately, however, insufficient data exist to allow no-effect levels to be characterized for either the respiratory or myocardial effects. Nor is there sufficient evidence to state with confidence no-effect levels for either the growth or shortened lifespan and altered blood chemistry effects observed in some studies with chronic oral exposure to antimony in the diet or drinking water.

HUMAN HEALTH EFFECTS

Essentially no information on antimony-induced human health effects has been derived from community epidemiology studies reflecting, to a large extent, the lack of any heretofore identified environmental health problems being associated with antimony. In order to project what might occur in regard to environmental health problems, then, it is necessary to draw upon the only available data bases, i.e., literature on effects observed with therapeutic or medicinal uses of antimony compounds and industrial exposure studies. In each type of literature some examples of acute toxic effects and others of a more chronic nature have been documented.

Therapeutic Uses

Various antimony compounds still are drugs of choice for treating schistosomiasis. The route of administration is generally intramuscular or intravenous. Fairhall and Hyslop (1947) reported that antimony is better tolerated when administered intravenously

than orally. These investigators indicated that death may result after an oral dose of 150 mg while 30 to 150 mg is recommended for intravenous treatment. The scope of accidental overdosing problems that once existed with therapeutic uses of antimonials is reflected by Khalil's (1936) estimates that a 0.2 percent mortality resulted from one million antimony treatments annually in Egypt.

Symptoms observed following accidental overdosing are illustrative of certain types of health effects seen at lower dose levels, albeit in less severe form.

Heart-related complications, convulsions, and severe vomiting were associated with an overdose of sodium antimonyl gluconate given to a 10-year-old African child (Sapire and Silverman, 1970). Severe myocardial involvement was indicated after the schistosomiasis patient had been given a dose of 300 mg daily for six days. Convulsions and vomiting occurred near the end of the course of treatment. During the convulsions, heart rate was rapid and irregular and the pulse was feeble and irregular. Multiple ventricular extrasystoles with runs of paroxysmal ventricular tachycardia were observed on the ECG trace. A diagnosis of acute antimony poisoning with cardiotoxicity was made. After initiation of chemotherapy, the ECG abnormalities persisted for 48 hours, although to a reduced degree. The patient thereupon reverted to sinus rhythm. Principal effects appeared in the ST segment and in the T-wave. Only occasional changes in the QRS axis were noted.

Effects on the Gastrointestinal System

Nausea and vomiting are symptoms most commonly reported. Zaki, et al. (1964) injected schistosomiasis patients intramuscu-

larly with a 10 percent solution of Astiban (Sb with a +3 valence), 3 to 5 ml per day for 5 days. Vomiting was seen in 45 percent of the patients; nausea, gastric discomfort, and/or anorexia was observed in 44 percent; and diarrhea in only 6 percent.

Effects on the Hepatic System

While impaired liver function may result in symptoms normally associated with gastrointestinal involvement, more severe liver damage is a rare complication in antimony therapy. However, McKenzie (1932) and O'Brien (1959) have attributed some fatalities to liver necrosis.

Routine clinical investigations of liver function, such as serum bilirubin, rarely are undertaken in antimony therapy. Several cases involving a simultaneous rise of SGOT and SGPT at the onset of therapy were reported by Woodruff (1969). Variations in serum ornithine carbanyl transferase, parallel to that of transaminases, were suggestive of a hepatic lesion (Spitaels and Bounameaux, 1966). These investigations concluded that a hepatic lesion is a central feature of antimony toxicity and that it is caused by a progressive accumulation of Sb in the liver.

Effects on the Cardiovascular System

Changes in the electrocardiogram (ECG) reading of heart action have been consistently associated with intravenous Sb therapy. Various degrees of suppression of the amplitude in the T-wave, inversion of the T-wave, and prolongation of the QT interval are the most typical changes described (Mainzer and Krause, 1940; Schroeder, et al. 1946; Davis, 1961; Sapire and Silverman, 1970; Abdalla and Badran, 1963). The T-wave changes seem to be the most

frequent, appearing in 100 percent of the treated patients in some studies. Changes that occur less frequently are: (1) diminution of amplitude of the QRS complex, (2) bradycardia, (3) changes in the ST segment, and (4) ventricular arrhythmias. While enzyme impairment, antimony deposits in the heart, autonomic nervous system dysfunction, and other functional impairments have been suggested as leading to ECG changes, they generally are not considered to be indicative of persistent cardiac damage (Schroeder, et al. 1946; Davis, 1961; Sapire and Silverman, 1970).

A description of the ECG changes following antimony sodium tartrate therapy was provided by Honey (1960). In all but one of the 59 patients, ECG changes were seen toward the end of the course of therapy. Changes ranged from very slight to severe. In the absence of a history of antimony sodium tartrate administration, the severe changes would have been interpreted as indicating severe myocardial disease. The effects described by Honey have also been seen upon therapy with other antimonial drugs (Mainzer and Krause, 1940; Schroeder, et al. 1946; Tarr, 1947; Abdalla and Badran, 1963; Germinaini, et al. 1963; Dancaster, et al. 1966; Sapire and Silverman, 1970; Waye, et al. 1962; Hsu, et al. 1960; Somers and Rosanelli, 1962; Awwaad, et al. 1961; Badran and Abdalla, 1967; O'Brien, 1959).

Honey (1960) indicated that the following changes were characteristic: the P-wave often becomes tall and broad, while R-wave voltage is significantly lowered. No changes in PR or QRS intervals were observed although the QT interval increased in most cases. The most characteristic abnormalities were in the ST seg-

ment and T-waves. The earliest change was a reduction in amplitude of the T-wave in all leads. In severely affected cases, the T-wave became completely inverted. No consistent change in pulse rate was observed, although one case of serious ventricular arrhythmia was seen. Honey theorized that the longest intervals were associated with sinus arrest or sinoatrial block.

The ECG changes that are observed have been associated with both trivalent and pentavalent antimonial therapy. Trivalent compounds are more widely used. The drugs most effective in the treatment of schistosomiasis also cause the greatest disturbance to the heart. The percentage of patients having altered ECGs has often approached 100 percent after intravenous administration of trivalent antimony potassium or sodium tartrate (Honey, 1960; Schroeder, et al. 1946; Tarr, 1947). Altered ECGs occur in less than 80 percent of those individuals receiving trivalent compounds intramuscularly.

ECG changes following treatment with pentavalent compounds have been infrequently observed. Administration of trivalent and pentavalent drugs to 30 patients with schistosomiasis or leishmaniasis resulted in flattened T-waves, anomalous QT intervals, and myocardial ischemia of the subepicardial layer. Only five patients received the pentavalent drugs (Germiniani, et al. 1963). Davis (1961) observed that ECG changes following treatment with pentavalent compounds are much less severe than with trivalent compounds. In part, this may be due to the observation that trivalent compounds are only slowly eliminated by the kidney, whereas pentava-

lent compounds are metabolized by the liver and are excreted more rapidly (Sapire and Silverman, 1970).

Lopez and da Cunha (1963) did not observe any treatment-related ECG alterations in patients receiving the pentavalent drug. The total dose of pentavalent Sb ranged from 4.95 to 19.35 gm given intravenously over 5 to 10 days. On the other hand, the total dose of trivalent antimony ranged from 214 to 510 mg given intravenously over 2 to 9 days. All patients given trivalent antimony sodium gluconate exhibited diffuse alterations in ventricular repolarization, seen primarily in the T-wave, and in one case, accompanied by a sinus tachycardia. In the group receiving m-methyl glucamine antimoniate (pentavalent), only one patient showed ECG changes. The arrhythmia observed was attributed to the patient's advanced case of kala-azar. Similarly, Tarr (1947) was unable to find ECG alterations in three patients treated with the pentavalent compounds, ethylstibamine or glucostibamine sodium. However, typical changes in the T-wave of patients given either of two trivalent compounds (antimony potassium tartrate or stibophen) were observed.

ECG changes in Egyptian adults, adolescents, and children treated with antimony dimercaptosuccinate (TWSb) have been reported by Abdalla and Badran (1963). The course of treatment consisted of five daily intramuscular injections of 6 mg TWSb/kg body weight (total dose = 30 mg/kg or 7.5 mg Sb/kg) administered to 25 adult patients. The patients had normal ECGs prior to treatment. ECGs were monitored after the completion of the treatment course. In five patients, ECGs also were performed 0.5 hours after the first, third, and fourth injections. Among the changes observed (number

of patients exhibiting effects are shown in parantheses) were: diminution in amplitude of the P-wave (12), prolongation of the PR interval (2), decrease in PR interval (4), decrease in the amplitude of the QRS complex (10), increase in amplitude of the QRS complex (1), slight depression of the ST segment (3), and T-wave changes (24). No changes in the ECG were observed immediately or up to two hours after the first injection. The effects of the treatment on the myocardium were cumulative; they started after the third dose and were more marked after the fourth and fifth doses. ECGs exhibited normal behavior within 4 to 6 weeks following treatment.

Davis (1961) found ECG abnormalities after treating 19 male African children or adolescents, ages 11 to 20, with antimony dimercaptosuccinate intravenously. The total dosage given for Schistosoma mansoni and S. haematobium ranged from 1.0 gm in five days to 2.0 gm in three days. ECGs were monitored before treatment, daily during treatment, and for the first two or three days after treatment. All patients exhibited inverted T-waves in one or more leads following treatment. Inversion was observed at different times, and no dose-response was ascertained. Maximum amplitude was observed on the last day of treatment or during the first three days after treatment. Persistent abnormalities were seen in 7 of 12 cases at 28 to 33 days and in two of five cases at 54 days after treatment. These abnormalities were either persistent inversion of the T-wave in the right unipolar precordial leads or the failure to regain their amplitude before treatment. Transitory prolongation of the QT_c interval was noted in 9 of 19 series of

recordings. The investigators found that 15 patients had isoelectric, or inverted, T-waves before treatment. These individuals exhibited the onset of frank inversion or an increase in the T-wave amplitude of inversion following treatment. The authors commented that T-wave inversion before treatment occurs among Africans of all ages and is a common finding among African children.

The ECG changes observed upon treatment were largely reversible over a period of weeks and roughly paralleled the excretion rate of Sb. It was suggested that temporary myocardial damage resulted from accumulation of trivalent Sb.

Honey (1960) suggests that Asians and Africans are more susceptible than Europeans to the cardiotoxic effects of Sb. Of 15 African or Asian patients, 11 had severe ECG changes while 7 of 45 Europeans had changes classified as "severe."

Huang, et al. (1960) noted a greater susceptibility to antimonial drugs among females as opposed to males. Severe cardiac arrhythmia was more frequently found in female patients, especially those undergoing menstruation or lactation. The investigators were not aware of any such episodes occurring in pregnant women.

Antimony dimercaptosuccinate treatment was observed by Abdalla and Badran (1963) to result in more marked ECG changes than when potassium antimony tartrate, another trivalent compound, was employed. Inversion of the T-wave occurred in 32 percent of those receiving TWSb but in only 10 percent of those receiving the tartrate compound.

Decreases in T-wave amplitude and elevations of the ST segment were observed in Egyptian patients receiving sodium antimony bis-

(pyrocatechol-2,4-disulfonate), a trivalent compound (Zaki, 1955). This compound also was used by O'Brien (1959) to treat 20 young, West African soldiers for schistosomiasis. The total dose of antimony given intravenously was 807.5 mg over a period of 20 days. One individual exhibited gross ventricular dysrhythmia. Recovery was complete after administration of British Anti-Lewisite. Near the end of treatment, all individuals had abnormal ECGs. Abnormalities were elevation of the ST segment followed by a sharp inversion of the T-wave in the right ventricular unipolar precardial leads. ECG traces were normal three months after treatment. Temporary heart muscle damage was suggested as a result of treatment.

A Stokes-Adams syndrome was observed by Dancaster, et al. (1966) in a 26-year-old female biharziac patient receiving antimony sodium gluconate. During the 24 hours following the fourth daily injection, she lost consciousness six times, and once she stopped breathing. The first ECG taken exhibited changes compatible with hypokalemia. The T-wave flattened and the U-wave was prominent. An ECG taken 24 hours later suggested inferior myocardial infarction. The ECG returned to normal over a period of six weeks. A direct effect of antimony on the myocardium or a coronary spasm caused by Sb was suggested. Similar case histories with other antimonial drug regimens are cited by Sapire and Silverman (1970), Waye, et al. (1962), Hsu, et al. (1960), and O'Brien (1959).

Woodruff (1969), Sapire and Silverman (1970), and Honey (1960) suggest that dose-response results are unclear. Hypersensitivity and the type of antimonial are more important factors than total dose. The most severe ECG changes have been found to occur with the

smallest doses. Honey (1960) noted that the action of antimony on the myocardium appeared to be cumulative as followed on an individual basis.

Lu and Liu (1963) reported that cardiac intoxication caused 70 to 97 percent of the reported antimony drug-related deaths, followed by hepatic or generalized intoxication. No data were given. Honey (1960) reported that cardiac edema and fragmentation of myocardial fibrillar structures were found upon autopsy on a person who died after 12 injections of antimony sodium tartrate. Total amount administered was 1.5 grams. The heart showed appearances of a very recent moderate-size myocardial infarction. The analyses for Sb were: blood, 0.17 mg/100 gm; liver, 0.20 mg/kg; skeletal muscle, 3.0 mg/kg; and heart muscle, 2.0 mg/kg.

The effect of antimonial therapy on heart rate was examined by Tarr (1947). An increase averaging 10 to 15 beats per minute was found in 48 treatment courses. A decrease averaging 10 to 15 beats per minute was found in 77 cases; no change was found in the remaining 56 cases. Tarr was unable to observe any relationship between the T-wave and heart rate changes. Others have failed to observe significant changes in heart rate in patients receiving antimonial drugs (Honey, 1960; Schroeder, et al. 1946; Abdalla and Badran, 1963; Waye, et al. 1962).

Effects on the Skin

Side effects resulting from antimony exposure or therapy include skin rashes, generalized urticaria, maculopapular eruptions, irritation around the eyes, and pruritis. Skin rashes appear in approximately 10 to 25 percent of the patients (Zaki, et al. 1964;

Hamad, 1969; Pedrique, et al. 1970). Skin irritation and rashes have most often been observed following exposure to antimony trioxide (Renes, 1953; Paschoud, 1964) and have usually been associated with hot environments during the summer months (McCallum, 1963). Antimony oxychloride, pentachloride, and trisulfide have not been reported to cause dermatitis.

Other Effects

Harris (1956) reported that therapeutic use of Faudin, an antimony compound, can cause acute hemolytic anemia. Erythrocytes gave a positive antiglobulin test. In vitro experiments demonstrated that serum factors capable of agglutinizing normal red cells and sensitizing them to become positive upon Coombs testings, as well as hemolyzing both trypsinized and normal red cells, could not be found unless the drug was present.

Trivalent compounds were associated with two cases of optic neuropathy associated with visual disturbances and indefinite fundus changes which occurred a few days following treatment (Forsyth, 1958).

Summary of Therapeutic Use Effects

As indicated above, gastrointestinal symptoms including severe nausea and vomiting are associated with acute high therapeutic exposures to antimonial compounds. In addition, rather severe myocardial symptoms and convulsions have also been seen with acute high doses of antimonial medicines, and some cases of deaths attributed to liver necrosis have been reported. With chronic exposures to lower dose levels of medicinal antimony compounds, myocardial effects stand out as being of key concern. Interesting-

ly, skin rashes and other irritative skin changes also occur in a certain percentage of patients during treatment with antimonial compounds; this provides evidence for skin changes being among health effects directly attributable to antimony and not necessarily being due to exposure to arsenic or other contaminants variously closely associated with antimony during the course of dermal or inhalation exposures in industrial situations.

Industrial Exposures

Antimony in nature commonly is found in deposits containing other elements and minerals such as arsenic, lead, selenium, and silica; it is therefore not unexpected that exposures to several such materials encountered along with antimony during its production and use tend to complicate interpretation of results from studies of health effects associated with industrial antimony exposures. Again, acute high exposures to antimony in occupational settings are illustrative in terms of highlighting the range of effects associated with the metal; many effects are observed in less severe form at lower, more chronic exposure levels.

General symptoms and the clinical pathology of antimony intoxication were discussed by Gocher (1945) in a survey of eight cases involving various industries. Many symptoms observed match these seen with overdosing with therapeutic uses of antimonials; such symptoms of acute industrial antimony poisoning include: (1) anorexia, (2) nausea, (3) vomiting, (4) diarrhea, (5) headache, (6) dizziness, and (7) irritation of the upper respiratory tract. In addition, rhinitis, bronchitis, gastric disturbances, colic, faintness, and feeble heart rates may be observed. Symptoms of

chronic severe intoxication may also include occipital headaches, dizziness, and muscular pain. Eosinophilia, moderate anemia, and leukopenia may be present. The degree to which Sb may be absorbed may be indicated by the reticulocyte count. An increase in reticulocytes always was found. Hemoglobin varied between 70 and 80 percent, and the red blood cell count fell between 3.8 and 5 million. Leukocytes averaged 7,800 in chronic cases and between 10,800 and 8,400 in acute cases. Glucosuria and albuminuria were present in half the cases.

Acute intoxication due to exposure to antimony pentachloride was reported by Cordasco and Stone (1973). A 39-year-old man was exposed to an unknown amount of the compound following a gas leak from a reactor. Second and third degree burns were reported. Respiratory distress was diagnosed upon hospital admission. Marked moist rales in both basal and mid-lung fields were noted. Pulmonary edema, persistent progressive respiratory distress, and respiratory acidosis ensued. Following long-term, intensive respiratory care, the patient improved.

Antimony trichloride was believed responsible for an episode of acute intoxication of seven men exposed to fumes. A pump leaking a hot mixture of antimony trichloride and hydrochloric acid was responsible. All workers had upper respiratory tract irritation which was attributed to the hydrochloric acid. Five of the men developed gastrointestinal disturbances, including abdominal pain and persistent anorexia. Red and white blood cell counts and hemoglobin levels were normal in four of the workers. Chest radiographs of all seven workers were normal.

Antimony in the urine was in excess of 1 mg/l in five of the seven men for up to two days after exposure. The highest concentration (one subject, two days after exposure) was 5.1 mg/l. Intermittent analyses on subsequent days indicated urine antimony content dropped rapidly. Subsequent air analyses three feet downwind from the pump revealed that the atmosphere contained up to 73 mg Sb/m^3 and 146 mg hydrochloric $acid/m^3$.

Among 78 workers exposed to antimony sulfide ore during mining, concentrating, and smelting operations, cases of nasal-septal perforations, laryngitis, tracheitis, and pneumonitis were reported in 3.5, 11.0, 10.0, and 5.5 percent of the workers, respectively (Renes, 1953). Rhinitis and dermatitis were reported in 20 percent of the workers. Among 7 of 9 workers severely affected, urinary levels of Sb ranged from trace amounts to 60 mg/100 ml. There was a progressive increase in the number of severe illnesses with increasing length of employment. Air levels of Sb ranged from 4.69 to 11.81 mg/m^3. Average arsenic levels were 0.73 mg/m^3. The size of the particles was less than 1 μ. Most cases of dermatitis were seen during a 1-week period of heavy exposure. The lesions were described as nodular and ulcerative. In those complaining of laryngitis, erosions or ulcerations of the vocal cords were always observed. Chest x-rays of six men, acutely ill from "heavy" exposure to smelter fumes, exhibited definite pneumonitis. No evidence of peripheral parenchymal pulmonary damage was found. Symptomatic treatment and removal from exposure for several days provided relief. Although emissions control measures were installed and lowered average Sb levels in the air to 6.8 mg/m^3 and arsenic to 0.54 mg/m^3, work-related illnesses were still occurring.

The symptoms observed by Renes were reported to be characteristic of both Sb and arsenic intoxication. However, the most common early signs of arsenic intoxication were not reported among these workers. In addition, higher arsenic exposures (in the electric furnace area) were not reflected by the more intense or increased numbers of illnesses in that area. Renes concluded that antimony trioxide, the predominant air contaminant, was responsible for the illnesses.

Respiratory and Dermal Effects

Effects on pulmonary function have been reported by Cooper, et al. (1968) among workers exposed to dust from antimony ore and antimony trioxide. In a total exposure population of 28 workers, pulmonary function studies were performed on 14 who had been exposed to antimony trioxide for periods of 1 to 15 years. Benign pneumoconiosis was found by roentgenography in 3 of 13 workers exposed to both types of dust. Five additional roentgenographs exhibited suspicious findings. The pattern of pneumoconiosis was one of small rounded and irregular opacities of the "p" and "s" types. Antimony excretion was variable and without correlation to the roentgen findings. Atmospheric concentrations of Sb monitored in 1966 at 36 plant locations ranged from 0.081 to 75 mg/m^3. Highest levels (138 mg/m^3) were associated with the bagging operations. Particle diameters were not reported. ECGs from seven workers (three of whom had pneumoconiosis) showed six with normal tracings and one with slight bradycardia. No correlations between urinary Sb levels (7 to 1,020 ug/l), roentgenographic abnormalities, and pulmonary function tests could be established.

Pneumoconiosis also was diagnosed by Le Gall (1969) in 10 of 40 furnace workers exposed to antimony oxide for periods of 6 to 40 years. Concentrations of antimony trioxide in the factory ranged from 0.3 to 14.7 mg/m^3. Most particles were reported to be smaller than 3 μm in diameter. Le Gall, however, reported that the ore used contained from 1 to 20 percent silica. Although there was no overt illness, the radiographs showed moderate, dense reticulonodular formations scattered through the pulmonary fields. Urine specimens from a few workers were analyzed, but Sb was not found. It is thus difficult to separate possible silica effects from presumed antimony effects reported here.

Pneumoconiosis and dermatitis in an unspecified number of antimony processing plant workers were found by McCallum (1963). The skin rashes consisted of pustules around sweat and sebaceous glands and resembled lesions associated with chicken pox or smallpox. Rashes were not observed on face, hands, or feet, but particularly were found on the forearms and thighs. Simple pneumoconiosis was diagnosed by radiographic examination. The lung changes, in nearly all cases, were symptomless. Two of the men subsequently developed tuberculosis. One had chronic bronchitis and respiratory obstruction. Pulmonary function tests suggested that the latter individual also had emphysema, but no pulmonary fibrosis was detected. Spot samples of urine from three with pneumoconiosis had Sb concentrations of 425, 480, and 680 ug/l. Air analyses at various plant locations (Newcastle-upon-Tyne, U.K.) indicated that Sb concentrations in the work environment generally exceeded 0.5 mg/m^3 with particles averaging less than 1 μm in diameter. Highest con-

centrations ($\approx$37 mg/m^3) were found when molten metal was poured. This study is especially valuable in linking the above effects to relatively purer antimony exposures than typically occur in other industrial settings.

Upon reinvestigation of this plant, McCallum (1967) discovered 26 cases of antimony pneumoconiosis. Of the 262 men employed at Newcastle-upon-Tyne, 44 had pneumoconiosis ascribed to Sb. All cases were of the simple type. One antimony worker who died from carcinoma of the lung was found to have had accumulations of dust particles and dust-laden macrophages lying in alveolar septa of his lungs and in perivascular tissues. No fibrosis or inflammation was seen, leading McCallum to suggest there was little or no reaction to Sb dust in the lung.

Using an improved method (in vivo x-ray spectroscopy) for detection and measurement of inhaled Sb_2O_3 dust retained in workers' intact lungs, McCallum, et al. (1970) screened 113 antimony process workers at Newcastle-upon-Tyne. Most workers examined had been employed at the site for less than 20 years and had worked at different operations for varying periods of time. An increase in pneumoconiosis was associated with a rise in the mean period of employment. The amount of Sb in the lungs of these workers ranged from undetectable levels to just over 11 mg/cm^2 of lung area. The individual having the highest lung level was employed at the factory for 35 years (16 of which he packed antimony trioxide).

An examination of 101 men employed at a Yugoslavian antimony smelter revealed 14 cases of simple pneumoconiosis (Karjovic, 1958). Emphysema and bronchitis were found in 22 workers, eight of

whom were less than 40 years old. There were four cases of tuberculosis. Other findings included catarrhal symptoms of the upper respiratory tract, conjunctivitis, and ulcerated nasal septae. No symptoms suggestive of damage to the gastrointestinal tract, liver, cardiovascular system, and central and peripheral nervous systems were observed. Dermatitis was found in 16 workers, 13 of whom worked at blast furnaces. The dermatitis was described as vesicular, varioliform, and efflorescent. The efflorescence underwent necrosis in the center and left hyperpigmented scars. In eight workers with pneumoconiosis (of 20 selected blast furnace workers), normal ventilatory function was exhibited in three cases and slightly reduced in four. Blood pressure values were reported as being somewhat lower in five of the eight workers with pneumoconiosis. No data were provided. ECGs and hepatograms were normal.

Due to the presence of other air contaminants (ferric oxide, silica, and arsenic trioxide), it is unclear to what extent antimony caused the observed findings. Antimony trioxide constituted 36 to 90 percent of the mixed dusts to which the workers were exposed. The particle sizes were predominantly under 0.5 μ.

In an antimony smelter in West Serbia, Yugoslavia, simple pneumoconiosis was found in 31 of 62 workers (Karajovic, et al. 1960). Emphysema and chronic bronchitis also were observed in some of the workers. Neither bronchio-pulmonary lesions nor symptoms of systemic poisoning were found, although skin effects were common.

Various lung-related disorders were found by Klucik, et al. (1962) in an investigation of workers at a Czechoslovakian antimony processing plant. These workers were exposed to smoke, antimony

trioxide dust, and antimony trisulfide for periods ranging from a few years to 28 years. The incidence was as follows: pharyngitis (76.5 percent), bronchitis and rhinitis (54.3 percent), pneumoconiosis (20.8 percent), symptoms of emphysema (41.9 percent), and perforations of the septa (33.2 percent). The average size of the dust and trioxide particles were 1.03 and 2.84 μm, respectively. Development of the pneumoconiosis ended at the micronodular size. It did not become complicated with tuberculosis.

Dermatitis, believed to result from the action of antimony trioxide on the dermis after dissolving in sweat and penetrating the sweat ducts, was reported by Stevenson (1965). Dermatitis was found in 23 of 150 workers exposed to SbO_3 at the Newcastle-upon-Tyne works. All affected workers were exposed to hot environments; 17 worked at the furnaces. The antecubital area was most often involved. Dermatitis subsided in 3 to 14 days after workers were transferred to cooler areas. Microscopic examination of the lesions revealed epidermal cellullar necrosis with associated acute dermal inflammatory cellular reaction. The lesions were found close to sweat ducts. Stevenson noted that SbO_3 is soluble in lactic acid, which is present in sweat in increased amounts following heavy exercise. Patch tests with dry SbO_3 or SbO_3 in water were negative.

Skin patch tests on 45 women and seven men with a mixture of powdered SbO_3 and 0.29 percent arsenic covered with moistened gauze pads were negative over a 3-week period (Linch and Sigmund, 1976). Antimony trioxide was not considered a primary skin irritant or a skin sensitizer.

Myocardial Effects

Heart abnormalities associated with occupational exposures to Sb have also been investigated.

Changes in ECG traces were correlated with exposure to Sb by Klucik and Ulrich (1960). However, concomitant exposure to arsenic may have contributed to the observed changes. Only ECG abnormalities and subjective complaints were correlated. Abnormal ECGs were found in 8 of 14 metal workers with frequent subjective complaints.

A decrease in blood pressure and ECG changes were found among a work force of 89 antimony production workers in the USSR (Beskrovnaya, 1972). More than half of the work force (average length of employment of 11 years) complained of cardiac pain. Decreased contractile force and lower electrical activity of the myocardium accompanied by increased excitability were found. Extrasystolic arrhythmia was observed in 12 workers; systolic noise was heard in 23. ECGs showed diminution of P-, R-, and T-waves and a simultaneous slowdown of intraventricular conductivity to 0.1 percent at 0.002 seconds. Balistocardiographs showed 12 cases evaluated as Brown's 3rd degree. The investigators concluded that diffuse damage to the ventricles of the myocardium and a diminution of its contractile ability were indicated.

Sudden death and heart complications associated with exposure to antimony trisulfide in a manufacturing setting were discussed by Brieger, et al. (1954). An increase in the number of sudden deaths among factory workers engaged in the manufacture of resinoid grinding wheels was observed after the use of lead was discontinued and antimony trisulfide substituted. Following replacement, six sudden

deaths and two deaths due to chronic heart disease occurred among 125 workers exposed for 8 to 24 months. Prior to replacement of lead, only one death (coronary thrombosis) occurred in 16 years in that department. Antimony trisulfide was found in air concentrations exceeding 3.0 mg/m^3.

Phenol formaldehyde resin also was used in the manufacturing process but workplace concentrations were not reported. In a clinical survey of 113 workers, ECG changes in 37 of 75 workers were found. These changes primarily involved the T-wave. Of the 113 men examined in the survey, 14 had blood pressures exceeding 150/80 mm and 24 had pressures lower than 100/70 mm. No mention was made of smoking, drinking, or medical histories of the workers. Following the cessation of use of antimony trisulfide, no additional deaths or abnormal cardiac effects were observed.

Carcinogenesis

An investigation of the role Sb may play in inducing lung cancer among antimony workers was conducted by Davies (1973). The study was initiated in 1962 after it was learned that a man engaged in the processing of antimony had died from lung cancer. A retrospective study found seven other deaths from lung cancer among antimony workers in the preceding eight years. Four of these men had worked at the Newcastle-upon-Tyne antimony works. The other three men had worked in an antimony processing plant that had discontinued operations. Smoking habits were not reported nor was information on the exact procedures used for computing the reported death rates; also the death rates observed were lower than expected rates for the workers.

Blood Effects

Symptoms of light and chronic intoxication were found by Rodier and Souchere (1957) in a study of 115 Moroccan antimony mine workers. A mean leukocyte count of 4,900 per mm^3 was found in 44 percent of the workers. A red blood cell count of less than 4 million per mm^3 was found in 47 percent of the workers. More than 1 gm of Sb per kg hair was found.

Reproduction and Development Effects

Female antimony smelter workers were evaluated by Belyaeva (1967) for gynecological disorders. A greater incidence of disorders was found among smelter workers than in a control group (77.5 percent v. 56 percent). Spontaneous late abortions occurred in 12 percent compared to 4.1 percent in controls. The birth weight of children born to exposed female workers was not different from those born to controls but weight began to lag behind at age three months and was significantly less at one year of age. The women were exposed to metallic antimony dust as well as antimony trioxide and pentoxide. Mean concentrations of antimony in the blood and urine of female workers were more than 10 times greater than in the control group. Average urine levels of Sb for exposed workers ranged from 2.1 to 2.9 mg/100 ml. Antimony also was found in breast milk (3.3 $\pm$ 2 mg/l), placental tissue (3.2 to 12.6 mg/100 mg), amniotic fluid (6.2 $\pm$ 2.8 mg/100 mg), and umbilical cord blood (6.3 $\pm$ 3 mg/100 ml).

Aiello (1955) observed a higher rate of premature deliveries among women workers in antimony smelting and processing. Premature deliveries occurred in 3.4 percent of the study group and in 1.2 percent of the controls. Women workers had frequent cases of dysmenorrhea as well as some cases of epistasis.

CRITERION FORMULATION

Existing Guidelines and Standards

At the present time, no standards exist regarding allowable amounts of antimony in food or water. This reflects the fact that only very small trace amounts of antimony have ever been found in food or water samples from United States surveys; this also reflects the general lack of any past public health problems associated with antimony exposures via food or water intake. The only present standards that exist, then, are those established for the protection of workers in occupational settings.

Existing occupational standards for exposure to antimony are reviewed in the National Institute for Occupational Safety and Health (NIOSH, 1978) criteria document, Occupational Exposure to Antimony. These standards apply most specifically to airborne antimony but may be useful for purposes of deriving a recommended standard for water.

As stated in the NIOSH (1978) document, the American Conference of Governmental Industrial Hygienists (ACGIH), in 1977, listed the TLV for antimony as 0.5 mg/m^3 along with a notice of intended change to a proposed TLV of 2.0 mg/m^3 for soluble antimony salts. The proposed TLV was based mainly on the reports of Taylor (1966) and Cordasco (1974) on accidental poisoning by antimony trichloride and pentachloride, respectively. Proposed limits of 0.5 mg/m^3 for handling and use of antimony trioxide and 0.05 mg/m^3 for antimony trioxide production, however, were also included in the ACGIH (1977) notice of intended changes.

The Occupational Safety and Health Administration earlier adopted the 1968 ACGIH TLV for antimony of 0.5 mg/m^3 as the Federal standard (29 CFR 1910.1000). This limit is consistent with limits adopted by many other countries as described in Occupational Exposure Limits for Airborne Toxic Substances - A Tabular Compilation of Values from Selected Countries, a publication released by the International Labor Office in 1977. The NIOSH (1978) document also presented a table of exposure limits from several countries, reproduced here as Table 3; the typical standard adopted was 0.5 mg/m^3, as indicated in Table 3. The 0.5 mg/m^3 level was also recommended as the United States occupational exposure standard by the NIOSH (1978) criteria document, based mainly on estimated no-effect levels for cardiotoxic and pulmonary effects.

Special Groups at Risk

At this time, none of the available information permits conclusive identification of populations at special risk for antimony exposure except, of course, for occupationally exposed individuals. All other types of general environmental exposures, from all media and sources, appear to represent essentially negligible antimony exposure levels for humans, as discussed earlier.

If antimony exposure levels were to reach substantially higher levels in the air or water, however, then individuals with existing chronic respiratory or cardiovascular disease problems would likely be among those at special risk in light of probable exacerbation of one or both types of health problems by antimony.

TABLE 3

Hygienic Standards of Several Countries for Antimony and Compounds in the Working Environment

Country	Standard (mg/m^3)	Qualifications
Finland	0.5	Not stated
Federal Republic of Germany	0.5	8-hour TWA
Democratic Republic of Germany	0.5	Not stated
Rumania	0.5	Not stated
USSR	0.5	For antimony dust
	0.3	For flourides and chlorides (tri-and pentavalent); obligatory control of HF and HCl
	1.0	For trivalent oxides and sulfides
	1.0	For pentavalent oxides and sulfides
Sweden	0.5	Not stated
USA	0.5	8-hour TWA
Yugoslavia	0.5	Not stated

Modified from Occupational Exposure Limits In Airborne Toxic Substances, International Labour Office (1977)

Basis for the Criterion

Summary of Health Effects

At the present time, there are essentially no existing community epidemiology studies that provide information on health effects associated with antimony exposure among the general population of the United States or other countries. This is primarily due, as indicated earlier, to the lack of any recognizable public health problems having been previously associated with environmental exposures to antimony. Rather, one is limited to extrapolating, as best as can be done, from human occupational health and animal toxicology studies.

Pulmonary, cardiovascular, dermal, and certain effects on reproduction, development, and longevity are among the health effects best associated with antimony exposure. The pulmonary effects, however, are almost exclusively associated with inhalation exposures and have much less relevance than the other effects in considering possible bases for development of criteria for a water standard. The pulmonary effects are, therefore, not considered here, but rather the main emphasis is placed on the latter types of effects listed.

Cardiovascular changes have been well associated with exposure to antimony and probably represent the most serious antimony-related human health effects demonstrated thus far. Specifically, in humans, various ECG changes, e.g., altered T-wave patterns, have been consistently observed following exposures to either trivalent or pentavalent antimonial compounds and have been interpreted as being indicative of at least temporary cardiotoxic effects of anti-

mony. Indications of even more severe, possibly permanent myocardial damage in humans have been obtained in the form of histopathological evidence of cardiac edema, myocardial fibrosis, and other signs of myocardial structural damage. Parallel findings of functional changes in ECG patterns and of histopathological evidence of myocardial structural damage have also been obtained in animal toxicology studies using controlled exposures to antimony compounds.

As for the other types of effects reasonably well associated with antimony exposures, only very limited data exist regarding such effects, and they are presently insufficient to allow definitive conclusions to be drawn regarding important exposure parameters determining their induction in humans. For example, certain skin irritation effects, e.g., rashes, have been noted to occur with high levels of occupational antimony exposure, especially under conditions of extreme heat; similar dermal effects have been reported for at least some patients undergoing therapeutic treatments with systemic injections of antimonials. There does not yet exist, however, any evidence to suggest that dermal effects would result from oral ingestion of antimony compounds. In regard to effects on reproduction, development, and longevity, the available evidence linking such effects to antimony is almost entirely derived from animal toxicology studies and consists primarily of data suggesting that: (1) prenatal exposures can interfere with conception, (2) chronic oral exposure via feeding can result in postnatal retardation of growth as indexed by body weight gain, and (3) chronic oral exposure via drinking water can induce alterations in certain blood chemistry parameters and significantly shorten

survival time or lifespan. Such effects, however, have not yet been well replicated in other animal studies; only very limited analogous antimony-induced effects on reproduction have yet been demonstrated to occur in humans.

In summary, myocardial effects are among the most serious and best characterized human health effects that can presently be linked with antimony exposure; as such, setting an ambient water criterion predicated on protecting the general public from antimony-induced myocardial effects is the most desirable course of action if sufficient information on dose-effect relationships for myocardial effects exists. Failing that, then, the very limited animal toxicology literature on reproduction, development, and longevity effects would offer an alternative basis.

Dose-Effect/Dose-Response Relationships

The previous section summarizes the very limited information presently available regarding a qualitative description of adverse health effects associated with antimony exposure. Ideally, the main objective of the present section would be to provide further information regarding the characterization of dose-effect/dose-response relationships that hold for the induction of the key health effects expected to provide a basis for setting a criterion for antimony. In regard to the definition of "dose-effect" and "dose-response" relationships, Pfitzer (1976) explains the distinction between effect and response in the following terms: "Effect is taken to indicate the variable change due to a dose in a specific subject; and "response" is the number of individuals in a group showing that effect, i.e., the number of "reactors" showing a

specific effect at a particular defined dose level." Unfortunately, it is virtually impossible to characterize key antimony-induced health effects in such quantitative terms due to the very limited data base that presently exists.

For example, data reported for the studies by Brieger, et al. (1954) suggest an inhalation no-effect level for myocardial effects as likely being around 0.5 mg/m^3. Air concentrations of antimony trisulfide ranging from 0.58 to 5.5 mg/m^3 (with most < 3.0 mg/m^3) were associated with the induction of altered ECG patterns and some deaths attributed to myocardial damage among certain antimony workers (Brieger, et al. 1954). Also, in parallel studies on animals, Brieger, et al. (1954), observed ECG alterations in rats and rabbits at antimony exposures of 3.1 to 5.6 mg/m^3, confirming that antimony per se can specifically produce myocardial effects of the type observed with the occupational exposures. Unfortunately for present purposes, however, no adequate data exist on oral exposures to antimony compounds which would support reasonable estimates regarding likely no-effect levels for the induction of myocardial effects via antimony ingestion. Nor is there sufficient information on relative absorption rates following oral or inhalation exposures to antimony to allow for extrapolation of likely dose-effect relationships for oral exposures from the limited inhalation exposure data. Consequently, it is presently impossible to recommend a water criterion level based on projected no-effect levels for myocardial damage.

The TLV for antimony is also inappropriate as a basis for a water quality criterion. It is clear from the reports used over

the years by ACGIH for setting an antimony TLV that the value is arrived at with a minimum of hard data. The reports, on careful reading, provide little information on the acute effects of antimonials by virtue of the fact that the agent(s) are the corrosive halides to which workers had very short accidental exposure. Cordasco (1974) tabulated data on three cases of pulmonary trauma in workers having industrial accidents involving antimony chloride. Another report by Taylor (1966) dealt with short exposure of workers to antimony chloride with one air level given for both hydrochloric acid and antimony chloride. Antimony trichloride and pentachloride are corrosive compounds which would be expected to have effects on the respiratory tract that reflect both hydrochloric acid injury as well as the hydrolyzed antimony effect. One would not expect any comparability in behavior or effect in man after oral intake.

In the absence of sufficient information to develop a criterion based on the TLV or known antimony myocardial effects in humans, the most viable alternative is to focus on animal toxicology studies demonstrating antimony-induced effects on reproduction, development, and longevity. From the animal studies, those pertaining to prenatal reproductive effects, e.g., Belyaeva (1967) and Casals (1972), employed inhalation exposures or systemic injections of antimony compounds, and their result cannot presently be extrapolated very well to project the likely impact of oral exposures. Similarly, the few human studies where effects on reproduction were reported (Belyaeva, 1967; Aiello, 1955) deal with inhalation exposures in occupational settings and cannot now be used to extrapolate likely oral exposure no-effect levels.

Turning to effects on postnatal development and longevity, a study by Gross, et al. (1955a) presents evidence for growth retardation occurring when rats were chronically fed diets containing two percent antimony trioxide, but a no-effect level for growth retardation cannot be deduced from the results reported. The studies by Schroeder (Kanisawa and Schroeder, 1969; Schroeder, et al. 1970) containing data on antimony effects on growth and longevity, on the other hand, indicate that oral exposure to 5 ppm of antimony in drinking water had no effect on the rate of growth of either rats or mice. The 5 ppm exposure level, however, was effective in producing significant reductions in life spans for animals of both species and altered blood chemistries for exposed rats. It is, therefore, recommended that the 5 ppm exposure level producing such effects be taken as a "lowest observed effect level" (LOEL) in animals that likely approximates the "no-effect" level for antimony induced effects on growth and longevity. Calculation of an acceptable daily intake (ADI) for man using the value of 5 mg/l of antimony and the uncertainty factor of 100, in view of no presently available human epidemiological data regarding such effect, would result in a recommended criterion of 145 µg/l.

$$\text{ADI} = \frac{5 \text{ mg/l} \times 25 \text{ ml/day/rat}}{100 \times 0.3 \text{ kg/rat}} = 4.17 \text{ µg/kg/day, and}$$

$$\text{ADI for 70 kg human} = 4.17 \times 70 = 292 \text{ µg/kg/day.}$$

If,

$$\text{Criterion} = \frac{\text{ADI}}{2\ 1 + (0.0065 \text{ kg} \times \text{F})},$$

then

$$\text{Criterion} = \frac{292\ \mu g/kg/day}{2\ l/day + (0.0065\ kg/day \times 1.0\ l/kg)}$$

$$= 145\ \mu g/l,$$

where

100 = uncertainty factor

2 = amount of water ingested, l/day

0.0065 = amount of fish/shellfish products consumed, kg/day

F = 1.0 Bioconcentration factor

Drinking water contributes 99 percent of the assumed exposure, while eating contaminated fish products accounts for one percent. The criterion level for antimony in ambient water can alternatively be expressed as 45 mg/l, if exposure is assumed to be from the consumption of fish and shellfish alone.

REFERENCES

Abdalla, A. and A. Badran. 1963. Effect of antimony dimercaptosuccinate on the electrocardiogram in patients treated for schistosomiasis. Am. Jour. Trop. Med. Hyg. 12: 188.

Abdalla, A. and M. Saif. 1962. Tracer Studies with Antimony-124 in Man. In: G.E.W. Walstenhalne and M. O'Conner (eds.), Bilharziasis. Little, Brown and Co., Boston. p. 287.

Aiello, G. 1955. Pathology of antimony. Folia Med. (Naples) 38: 100. (Ital.)

American Conference of Governmental Industrial Hygienists. 1977. Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1977. Cincinnati, Ohio.

Arthur D. Little Co., Inc. 1978. Report on antimony for Off. Tech. Serv., U.S. Environ. Prot. Agency.

Awwaad, S., et al. 1961. The effect of TWSb on the electrocardiogram of children suffering from urinary bilharziasis. Am. Jour. Trop. Med. Hyg. 10: 365.

Badran, A.M. and A. Abdalla. 1967. Treatment of schistosomiasis in cardiac patients by weekly injections of sodium antimony dimercaptosuccinate. Jour. Egypt Med. Assoc. 50: 360.

Bahner, C.T. 1954. Localization of antimony in blood. Proc. Soc. Exp. Biol. Med. 86: 371.

Belyaeva, A.P. 1967. The effect of antimony on reproduction. Gig. Truda Prof. Zabol. 11: 32.

Beskrovnaya, B.M. 1972. Condition of the cardiovascular system in chronic antimony poisoning. Sov. Zdravookhr. Kirg. Issue 1: 11. (Rus.)

Bradley, W.R. and W.G. Fredrick. 1941. The toxicity of antimony -- Animal studies. Ind. Med. (Indr. Hyg. Sec.) 2: 15.

Brady, F.J., et al. 1945. Localization of trivalent radioactive antimony following intravenous administration to dogs infected with Dirofelaria Immites. Am. Jour. Trop. Med. 25: 103.

Brieger, H., et al. 1954. Industrial antimony poisoning. Ind. Med. Surg. 23: 521.

Brune, O., et al. 1980. Distribution of 23 elements in kidney, liver, and lung of a control group in northern Sweden and of exposed workers from a smelter and refinery. Sci. Total Environ. (In press)

Callaway, H.M. 1969. Antimony. In: The Encyclopedia Britannica. Ency. Brit., Inc., Chicago, Illinois. 2: 20.

Campello, A.P., et al. 1970. Studies of schistosomicides antimonials on isolated mitochondria. I. Sodium antimony gluconate (Triostib). Biochem. Pharmacol. 19: 1615.

Casals, J.B. 1972. Pharmacokinetic and toxicological studies of antimony dextran glycoside (RL-712). Br. Jour. Pharmacol. 46: 281.

Clemente, G.F. 1976. Trace element pathways from environment to man. Jour. Radioanal. Chem. 32: 25.

Cooper, D.A., et al. 1968. Pneumoconiosis among workers in an antimony industry. Am. Jour. Roentgenol. Radium Ther. Nucl. Med. 103: 495.

Cordasco, E.M. 1974. Newer concepts in the management of environmental pulmonary edema. Angiology. 25: 590.

Cordasco, E.M. and F.D. Stone. 1973. Pulmonary edema of environmental origin. Chest. 64: 182.

Dancaster, D.P., et al. 1966. Stokes-Adams attacks following sodium antimonylgluconate (Triostam). S. Afr. Med. Jour. 40: 1029.

Davies, T.A.L. 1973. The health of workers engaged in antimony oxide manufacture -- A statement. Dept. Employment, Employment Med. Adv. Serv. (London)

Davis, A. 1961. The effect of antimony dimercaptosuccinate on the electrocardiogram. Br. Heart Jour. 23: 291.

Davison, R.L., et al. 1974. Trace elements in fly ash -- Dependence of concentration on particle size. Environ. Sci. Tech. 8: 1107.

Dernehl, C.U., et al. 1945. Animal studies on the toxicity of inhaled antimony trioxide. Jour. Ind. Hyg. Toxicol. 27: 256.

Djuric, D., et al. 1962. The distribution and excretion of trivalent antimony in the rat following inhalation. Arch. Gewerbepath. Gewerbehyg. 19: 529.

El-Bassouri, M., et al. 1963. Treatment of active urinary schistosomiasis in children with sodium antimony dimercapto succinate by the slow method. Trans. R. Soc. Trop. Med. Hyg. 57: 136.

Elinder, C.G. and L. Friberg. 1979. Antimony. In: L. Friberg (ed.), Handbook of Toxicology of Metals. Elsevier/North Holland Biomedical Press, Amsterdam. p 283.

Fairhall, L.T. and F. Hyslop. 1947. The toxicology of antimony. Pub. Health Rep. Suppl. No. 195.

Felicetti, S.W., et al. 1974a. Metabolism of two valence states of inhaled antimcny in hamsters. Am. Ind. Hyg. Assoc. Jour. 355: 292.

Felicetti, S.W., et al. 1974b. Retention of inhaled antimony-124 in the beagle dog as a function of temperature of aerosol formation. Health Phys. 26: 525.

Flassel, C.P. 1977. Metals as mutagens. Adv. Exp. Med. Biol. 91: 117.

Forsyth, D.M. 1958. Visual disturbances associated with trivalent antimony salts -- A report of two cases. Br. Med. Jour. 2: 1272.

Germiniani, H., et al. 1963. Electrocardiographic changes observed in patients treated with antimony compounds. Arq. Bras. Cardiol. 16: 299. October (Por.)

Girgis, G.R., et al. 1965. Acute tolerance of mice to tartar emetic. Toxicol. Appl. Pharmacol. 7: 727.

Gocher, T.E.P. 1945. Antimony intoxication. Northwest Med. 44: 92.

Gross, P., et al. 1952. Experimental endogenous lipoid pneumonia. Am. Jour. Pathol. 28: 211.

Gross, P., et al. 1955a. Toxicological study of calcium halophasphate phosphors and antimony trioxide. I. Acute and chronic toxicity and some pharmacological aspects. Arch. Ind. Health. 11: 473.

Gross, P., et al. 1955b. Toxicologic study of calcium halophosphate phosphors and antimony trioxide. II. Pulmonary studies. AMA Arch. Ind. Health. 11: 479.

Hamad, B. 1969. Trial of Astiban in treating university students in the Sudan. Jour. Trop. Med. Hyg. 72: 228.

Harris, J.W. 1956. Studies on the mechanism of a drug-induced hemolytic anemia. Jour. Lab. Clin. Med. 47: 760.

Hirayama, A. 1959a. Fate of antimony introduced into the body. Osaka Shiritsu Diagaku Igaku Zasshi. 8: 596.

Hirayama, A. 1959b. Studies on the normal limits of antimony in blood, urine, and feces among healthy Japanese urban inhabitants. Jour. Osaka City Med. Cen. 8: 609. (Jap.)

Hock, A., et al. 1975. Trace element concentration in human brain. Activation analysis of cobalt, iron, rubidium, selenium, zinc, chromium, silver, cesium, antimony and scandium. Brain. 98: 49.

Hogenfeldt, K.B., et al. 1977. Trace elements in the human endometrium and decidua. Acta Endocrinol. 85: 406.

Honey, M. 1960. The effects of sodium antimony tartrate on the myocardium. Br. Heart Jour. 22: 601.

Hsu, J.K., et al. 1960. Sodium antimony dimercaptosuccinate (Sb-58) in treatment of Schistosomiasis japonica. Chinese Med. Jour. 80: 530.

Huang, M.H., et al. 1960. Cardia arrhythmias in tartar emetic intoxication. Chinese Med. Jour. 80: 319.

Internatinal Commission on Radiological Protection. 1960. Report of I.C.R.P. Committee II on permissible dose for internal radiation (1959). Health Phys. 3: 189.

International Labor Office. 1977. Occupational exposure limits for airborne toxic substances -- A tabular compilation of values from selected countries. Occup. Safety Health Ser. No. 37, U.N. Int. Labor Off., Geneva.

James, L.F., et al. 1966. Effects of sublethal doses of certain minerals on pregnant ewes and fetal development. Am. Jour. Vet. Res. 27: 132.

Kanematsu, K. and T. Kada. 1978. Mutagenicity of metal compounds. Mutat. Res. 53: 207.

Kanisawa, M. and H.A. Schroeder. 1969. Life term studies on the effect of trace elements of spontaneous tumors in mice and rats. Cancer Res. 29: 892.

Karajovic, D. 1958. Pneumoconiosis in Workers at an Antimony Smelting Plant. In: Proceedings of the 12th Int. Congr. Occup. Health, Helsinki. 3 370. (Ger.)

Karajovic, D., et al. 1960. Silicoantimonosis. Arch. f. Gerwerbepath. Gewerbehyg. 17: 651. (Ger.)

Kennedy, J.H. 1966. Analysis of diseased and normal lung tissue for trace antimony content by neutron activation analysis. Am. Jour. Med. Sci. 251: 75.

Khalil, M.B. 1936. Individual variation in the excretion of drugs as an important factor in their therapeutic results. A practical method for detecting the schistosomiasis cases with so-called idiosyncrasy to antimony to avoid fatalities and complication. Jour. Egypt Med. Assoc. 19: 285.

Klucik, I. and L. Ulrich. 1960. Electrocardiographic examination of workers in an antimony metallurgical plant. Prac. Lek. 12: 236. (Czec.)

Klucik, I., et al. 1962. Lesions of the respiratory tract and the lungs caused by pulverulent antimony trioxide. Prac. Lek. 14: 363. (Czec.)

Kostic, K., et al. 1977. Determination of some trace elements in different organs of normal rats. Jour. Radioanal. Chem. 37: 405.

Le Gall. 1969. Pneumoconiosis and antimony. Arch. Mal. Prof. 30: 361. (Fre.)

Levina, E.N. and M.P. Chekunova. 1965. Toxicity of antimony halides. Fed. Proc. 24: T608.

Lievens, P., et al. 1977. The distribution of trace elements in normal human liver determined by semi-automated radiochemical neutron activation analysis. Jour. Radioanal. Chem. 37: 483.

Linch, A.L. and J.M. Sigmund. 1976. Antimony trioxide -- Industrial hygiene evaluation of a manufacturing operation. Presented before the 16th Annu. Am. Ind. Hyg. Conf., Atlanta, May 16-21.

Lopez, M. and A.S. da Cunha. 1963. Electrocardiographic course in patients treated with trivalent and pentavalent antimonials. Hospital (Rio de Janeiro) 63: 919. (Por.)

Lu, S.T. and H. Liu. 1963. A survey of short-course antimony tartrate therapy for Schistosomiasis japonica in China. Chinese Med. Jour. 82: 46.

Maeda, T. 1934. The influence of various heavy metallic salts on the glutathione in blood. Rolia Pharmacol. 18: 132. (Jap.)

Mainzer, R. and M. Krause. 1940. Changes of the electrocardiogram appearing during antimony treatment. Trans. R. Soc. Trop. Med. Hyg. 33: 405.

Mansour, T.E. and E. Bueding. 1954. The actions of antimonials on glycolytic enzymes of Schistosoma mansoni. Br. Jour. Pharmacol. 9: 459.

Matthews, C.M.E. and G. Molinaro. 1963. A study of the relative value of radioactive substances used for brain tumor localization and of the mechanism of tumor: brain concentration, uptake in transplantable fibrosarcoma, brain and other organs in the rat. Br. Jour. Exp. Pathol. 44: 260.

McCallum, R.I. 1963. The work of an occupational hygiene service in environmental control. Ann. Occup. Hyg. 6: 55.

McCallum, R.I. 1967. Detection of antimony in process workers' lungs by x-radiation. Trans. Soc. Occup. Med. 17: 134.

McCallum, R.I., et al. 1970. Measurement of antimony oxide dust in human lungs *in vivo* by x-ray spectrophotometry. Inhaled Particles. Proc. 3rd Int. Symp. 2: 611.

McKenzie, A. 1932. Fatalities following the administration of intravenous tartar emetic. Trans. R. Soc. Trop. Med. Hyg. 25: 407.

Minkina, N.A., et al. 1973. State of adrenals and biogenic amines under the effect of antimony and lead. Gig. Tr. Prof. Zabol. 17: 21. (Rus.)

Molokhia, M.M. and H. Smith. 1967. Trace elements in the lung. Arch. Environ. Health. 15: 745.

Molokhia, M.M. and H. Smith. 1969. Tissue distribution of trivalent antimony in mice infected with *Schistosoma mansoni*. Bull. WHO 40: 123.

Murthy, G.K., et al. 1971. Levels of antimony, cadmium, chromium, cobalt, manganese and zinc in institutional total diets. Environ. Sci. Tech. 5: 436.

National Academy of Sciences. 1977. Arsenic. Washington, D.C.

National Institute for Occupational Safety and Health. 1978. Occupational exposure to antimony. U.S. Dept. Health, Edu. Welfare.

Ness, A.T., et al. 1947. Anomalous distribution of antimony in white rats following the administration of tartar emetics. Jour. Pharmacol. Exp. Ther. 190: 174.

Nixon, G.S., et al. 1967. Estimates of antimony in human enamel by activation analysis. Caries Res. 1: 327.

O'Brien, W. 1959. The effects of antimony on the heart. Trans. R. Soc. Trop. Med. Hyg. 53: 482.

Otto, G.F. and T.H. Maren. 1950. Chemotherapy of filariasis. VI. Studies on the excretion and concentration of antimony in blood and other tissues following the injection of trivalent and pentavalent antimonials into experimental animals. Am. Jour. Hyg. 51: 370.

Paschoud, J.M. 1964. Clinical notes on eczemas from occupational contact with arsenic and antimony. Dermatologica. 129: 410. (Fre.)

Paton, G.R. and A.C. Allison. 1972. Chromosome damage in human cell cultures induced by metal salts. Mutat. Res. 16: 332.

Pedrique, M.R., et al. 1970. Clinical experiences with antimonyl-dimethylcysteimo-tartrate (NAP) in a rural population infected with Schistosoma mansoni. Ann. Trop. Med. Parasitol. 64: 255.

Pfitzer, E.A. 1976. General Concepts and Definitions for Dose-Response and Dose-Effect Relationship of Toxic Metals. In: G.F. Nordberg (ed.), Effects and Dose-Response Relationships of Heavy Metals. Elsevier, Amsterdam. p. 140.

Pribyl, E. 1944. On the nitrogen metabolism in experimental sub-acute arsenic and antimony poisoning. Jour. Biol. Chem. 74: 775.

Rasmussen, E.G. 1974. Antimony, arsenic, bromine and mercury in enamel from human teeth. Scand. Jour. Dent. Res. 82: 562.

Renes, L.E. 1953. Antimony poisoning in industry. AMA Arch. Ind. Hyg. Occup. Med. 7: 99.

Rodier, J. and G. Souchere. 1957. A study of antimony intoxica-tion in the mines of Morocco. Arch. Mal. Prof. 18: 662. (Fre.)

Sapire, D.S. and N.H. Silverman. 1970. Myocardial involvement in antimonial therapy -- A case report of acute antimony poisoning with serial ECG changes. S. Afr. Med. Jour. 44: 948.

Schroeder, E.F., et al. 1946. Effect of antimony on the electro-cardiogram. Am. Jour. Med. Sci. 212: 697.

Schroeder, H.A. 1966. Municipal drinking water and cardiovascular death rates. Jour. Am. Med. Assoc. 195: 81.

Schroeder, H.A. 1970. A sensible look at air pollution by metals. Arch. Environ. Health. 21: 798.

Schroeder, H.A. and L.A. Kraemer. 1974. Cardiovascular mortality, municipal water and corrosion. Arch. Environ. Health. 28: 303.

Schroeder, H.A., et al. 1970. Zirconium, niablium, antimony and lead in rats: Life-term studies. Jour. Nutr. 100: 59.

Smith, S.E. 1969. Uptake of antimony potassium tartrate by mouse liver slices. Br. Jour. Pharmacol. 37: 476.

Somers, K. and J.D. Rosanelli. 1962. Electrocardiographic effects of antimony dimerxapto-succinate (Astiban). Br. Heart Jour. 24: 187.

Spitaels, J.M. and Y. Bounameaux. 1966. Toxicite du dimercapto-succinate d'antimoine. Contribution a l'etude des reactions hepatiques par dosae de l'ornithine carbonyl transferase serique. Ann. Soc. Belge Med. Trop. 46: 697. (Fre.)

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3.

Stevenson, C.J. 1965. Antimony spots. Trans. St. John's Hosp. Dermatol. Soc. 51: 40.

Sumino, K., et al. 1975. Heavy metals in normal Japanese tissues. Arch. Environ. Health. 30: 487.

Tanner, J.T. and M.H. Friedman. 1977. Neutron activation analysis for trace elements in foods. Jour. Radioanal. Chem. 37: 529.

Tarr, L. 1947. Effect of the antimony compounds, fuadin and tartar emetic on the electrocardiogram of man -- A study of the changes encountered in 141 patients treated for schistosomiasis. Ann. Intern. Med. 17: 970.

Taylor, P.J. 1966. Acute intoxication from antimony trichloride. Br. Jour. Ind. Med. 23: 318.

Thomas, R.G., et al. 1973. Retention patterns of antimony in mice following inhalation of particles formed at different temperatures. Proc. Soc. Exp. Biol. Med. 144: 544.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency, Contract No. 68-01-4646.

U.S. EPA. 1980. Seafood consumption data analysis. Stanford Research Institute International, Menlo Park, California. Final report, Task 11. Contract No. 68-01-3887.

Waitz, J.A., et al. 1965. Physiological disposition of antimony after administration of ^{124}Sb-labeled tartar emetic to rats, mice and monkeys and the effects of tris (p-amino phenyl) carbonium pamoate on this distribution. Bull. WHO. 33: 537.

Waye, J.D., et al. 1962. Cardiotoxic effects of antimony dimercaptosuccinate in schistosomiasis with special reference to coexistent hepatic dysfunction. Am. Jour. Cardiol. 10: 829.

Wester, P.O. 1965. Concentration of 24 trace elements in human heart tissue determined by neutron activation analysis. Scand. Jour. Clin. Lab. Invest. 17: 357.

Woodruff, A.W. 1969. Comparative value of some currently used antischistoserual drugs. Ann. N.Y. Acad. Sci. 160: 650.

Woolrich, P.F. 1973. Occurrence of trace metals in the environment: An overview. Am. Ind. Hyg. Assoc. Jour. 34: 217.

Zaki, A.A. 1955. A preliminary study of the effect of intensive doses of antimony on the heart. Trans. R. Soc. Trop. Med. Hyg. 49: 385.

Zaki, M.H., et al. 1964. Astiban in Schistosomiasis mansoni: A controlled therapeutic trial in a nonendemic area. Am. Jour. Trop. Med. Hyg. 13: 803.